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Synthesis and Reactions of Some Tetrahydroquinolizinium Salts. Possible Precursors to Cycl[3.3.3]azine

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Several 6-methyl-4-substituted 1,2,3,4-tetrahydroquinolizinium salts have been prepared from suitably substituted 2-picolines. As these compounds are potential intermediates in the synthesis of cycl[3.3.3]azine, several pertinent reactions were studied with this objective in mind. All attempts, however, were unsuccessful and reasons for the failures are discussed.

The nitrogen heterocycle **1**, given the trivial names cycl[3.3.3]-azine[1] and tricyclazine,[2] is of considerable

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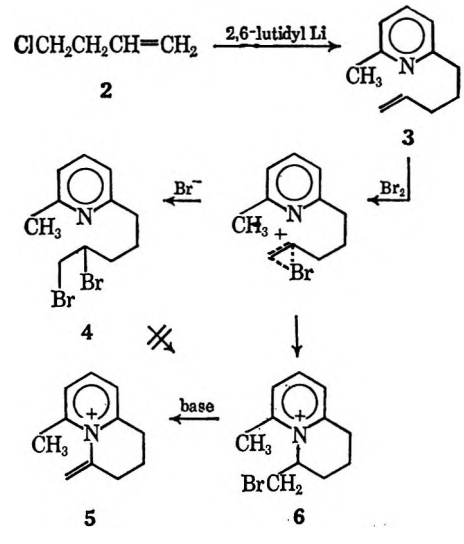
theoretical interest,[1,3] and has been the subject of much synthetic study.[2,4-8] We now report some of our work on 1,2,3,4-tetrahydroquinolizinium salts which are potential precursors of compound **1**.

A. The Pentenylpicoline[9] Route.—Pentenylpicoline **3** was prepared in two ways, 1-chlorobut-3-ene[10] (**2**) (see Scheme I), on reaction with 2,6-lutidyllithium, gave the same product **3**, as was obtained from the reaction of 1-bromopent-4-enyllithium[11] with 2-picoline.

Treatment of **3** with bromine resulted in the formation of two products **4** and **6**. Compound **4** was a high boiling oil, whereas **6** was an isomeric white salt probably formed by simultaneous bromination and cyclization of the olefin. Compound **4** could not be converted into **6** under the reaction conditions, nor could any conditions be found for this transformation.

SCHEME I



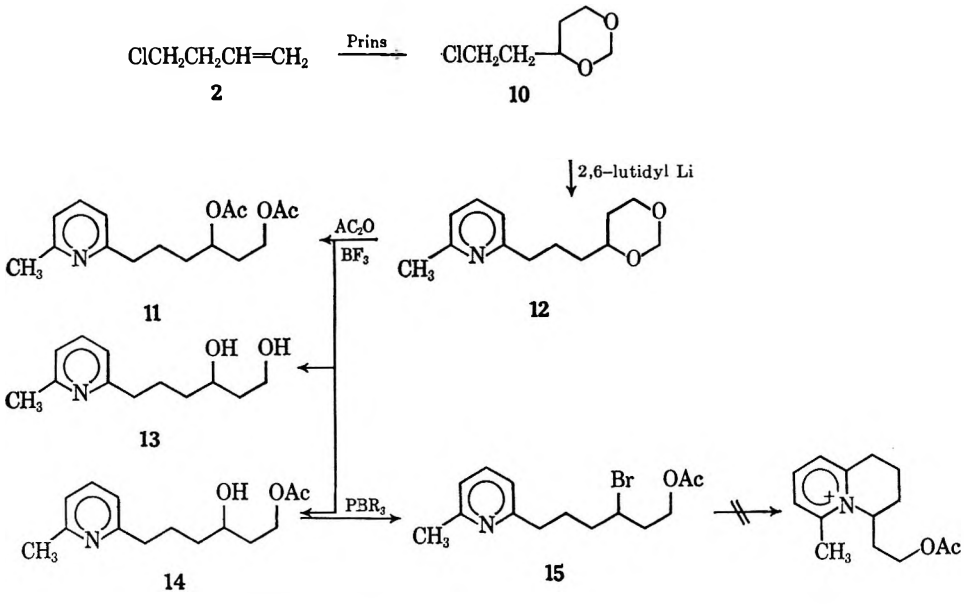
Treatment of the salt **6** with aqueous sodium cyanide yielded a salt which was isolated as the perchlorate, and which from spectral evidence appeared to have no nitrile group. Nmr evidence suggested that the new salt was the dehydrobromination product, 6-methyl-4-methylene-1,2,3,4-tetrahydroquinolizinium (**5**) perchlorate which could also be obtained when sodium carbonate was used instead of sodium cyanide.

In retrospect, it is not surprising that the observed elimination occurred as the bromine atom which was to be displaced would be directed away from the methyl group in the 6 position thus being effectively shielded against nucleophilic displacement by cyanide, and also, the hydrogen in the 4 position is expected to be relatively acidic as it is α to a positively charged nitrogen.

The reaction of the salt **6** with base or cyanide ion could be conveniently followed by nmr and some

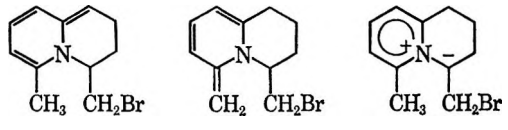
(1) R. J. Windgassen, Jr., W. W. Saunders, Jr., and V. Boekelheide, *J. Amer. Chem. Soc.*, **81**, 1459 (1959).
(2) V. Boekelheide and W. G. Gall, *J. Org. Chem.*, **19**, 499 (1954).
(3) R. D. Brown and B. A. W. Coller, *Mol. Phys.*, **2**, 158 (1959).
(4) H. V. Hansen and E. D. Amstutz, *J. Org. Chem.*, **28**, 393 (1963).
(5) I. Murskoshi, A. Kubo, J. Saito, and J. Haginina, *Chem. Pharm. Bull.* (Tokyo), **12**, 747 (1964).
(6) V. Boekelheide, H. Fritz, J. M. Ross, and H. X. Kaempfen, *Tetrahedron*, **20**, 33 (1964).
(7) W. K. Gibson and D. Leaver, *Chem. Commun.*, **1**, 11 (1965).
(8) D. Leaver and J. D. R. Vass, *J. Chem. Soc.*, 1629 (1965).
(9) The term pentenylpicoline, used throughout this text, should be taken to mean 1-[2-(6-methylpyridyl)]-pent-4-ene (**3**).
(10) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1952).
(11) Prepared by standard methods[12-14] from tetrahydrofurfuryl alcohol.
(12) I. A. Brooks and H. R. Snyder, *Org. Syn.*, **25**, 84 (1945).
(13) F. B. LaForge, N. Green, and W. A. Gersdorff, *J. Amer. Chem. Soc.*, **70**, 3707 (1948).
(14) H. Gilman, F. W. Moore, and O. Baine, *ibid.*, **63**, 2479 (1941).

SCHEME II



interesting observations were made. The salt was dissolved in deuterium oxide and its nmr spectrum was measured. Anhydrous potassium carbonate was added and the spectra were observed at intervals. The first observation was that the triplet centered at τ 6.7 quickly disappeared, suggesting that the hydrogens in the 1 position were undergoing base-catalyzed exchange with the solvent; next, the singlet at τ 7.13 disappeared suggesting that deuteration of the 6-methyl group was occurring; and, finally, the broad absorption at τ *ca.* 4.7 and the doublet at 6.14 (J = 8 Hz) both disappeared at the same rate to give way to another pair of absorptions at 4.22 and 4.60.

The order of the acidities (1 proton > methyl proton > 4 proton) can be understood by a consideration of the stability of the three conjugate bases **7**–**9** which



7 **8** **9**

would be the major contributing forms to the respective bases. Structure **9** in which there must always be charge separation would be least stable while steric effects would account for the relative stabilities of **7** and **8**.

The greater ease of removal of a proton from the 1 position in **6** than from the 6-methyl group may be of importance in later attempts to form the third ring in the cyclazine skeleton and may lead to an unwanted azabicyclo[2.2.2]octane. It is also of interest that **8** did not cyclize to a hexahydrocycl[3.3.2]azine.

B. The 1,3-Dioxane Route.—The above route failed in the attempt to add the final carbon atom to the bicyclic system. To overcome this difficulty a method was investigated whereby sufficient carbon atoms were incorporated into the system prior to cyclization. The acidity of the 2-methyl protons in substituted pyridines and of 6-methyl protons in quinolizinium salts make 2,6-lutidine an attractive starting point in any such synthesis. A conveniently protected substrate was considered to be 4-(2-chloroethyl)-1,3-dioxane which was readily prepared from 1-chlorobut-3-ene by a modification of the Prins reaction.[15] By performing the acid-catalyzed addition of formaldehyde to the olefin **2** in ether, the yield of the major by-product, 5-chloropentane-1,3-diol, could be kept to a minimum. The product **10** reacted smoothly with 2,6-lutidyllithium to yield **12** (Scheme II), the structure of which was substantiated by spectral data.

Cleavage of the metadioxane ring in **12** was most conveniently accomplished by the mild method of Youssefyeh and Mazur[16] which not only provided an effective procedure for the metadioxane ring opening, but partial hydrolysis of the diacetate produced gave as the major product the hydroxyacetate **14**, in which the primary hydroxyl was protected against further reaction in the next step. Chromatographic separation of the reaction products also gave **11** (15%) and the diol **13** (5%). Treatment of **13** or **14** with acetic anhydride also gave the diacetate **11**.

The hydroxyacetate **14** was treated with phosphorus tribromide to give a small yield of the corresponding bromide **15** which could be reconverted into **14** by hydrolysis in aqueous dioxane containing silver perchlorate. All attempts to cause the bromide **15** to cyclize were to no avail and this route was thus abandoned.[17]

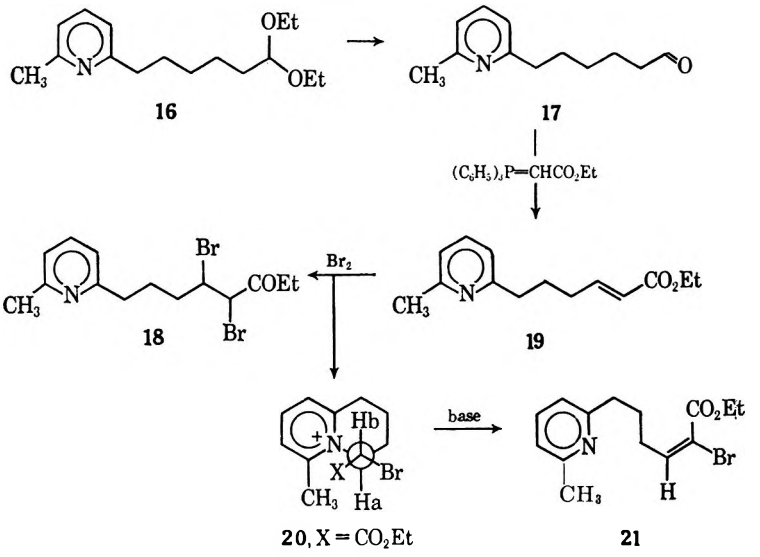
C. The α,β-Unsaturated Ester Route.—As is evident from the two approaches discussed, the displacement of a side-chain bromine atom by the nitrogen of a 2,6-disubstituted pyridine is not a practicable approach to the tetrahydroquinolizinium nucleus. However, the reaction of pentenylpicoline with bromine has shown that cyclization during bromination of a suitably situated double bond is certainly feasible and the accessibility of olefins *via* the Wittig reaction made this appear a most attractive route.

(15) H. J. Prins, *Proc. Acad. Sci.* (Amsterdam), **22**, 51 (1919).

(16) R. D. Youssefyeh and Y. Mazur, *Tetrahedron Lett.*, **26**, 1287 (1962).

(17) Two objections could have been raised against this method: (a) in view of the failure of **4** to cyclize, **15** might have been expected to behave similarly; and (b) the relative acidities of the methyl and methylene protons in **6** leave the mode of closure of the third ring open to speculation. In anticipation of these objections it is pointed out that this route was started well before the above results became known.

SCHEME III



β-Chloropropionaldehyde acetal[18] was treated with 2,6-lutidyllithium to yield the acetal **16** which upon hydrolysis gave the aldehyde **17** (Scheme III).

Of the Wittig reagents suitable for condensation with aldehyde **17**, that derived from ethyl bromoacetate was considered most desirable, particularly in view of ease with which it could be prepared.[19]

On reaction of the phosphorane with the aldehyde **17** a product was obtained which showed ultraviolet and infrared absorptions and an nmr spectrum compatible with the *trans* α,β-unsaturated ester **19** expected from the Wittig reaction.

Treatment of **19** with bromine in aqueous dioxane gave two products, a high boiling oil, tentatively assigned the structure **18** on the basis of its mass spectrum and method of preparation, and a white salt which was assigned the structure **20**.

When **20** was treated with base, closure of the third ring did *not* occur but instead, the sole product isolated in good yield was **21**. It was of interest to obtain a qualitative estimate of the relative rates of proton removal from the 4-methyl group and the position α to the ester, as cyclization of **20** to a tricyclic nucleus would require that the former reaction should occur at a measurable rate. The reaction in deuterium oxide was studied by nmr and the only detectable reaction was that yielding **21**, there being a complete absence of deuterium exchange at the 4-methyl group.

Experimental Section[20]

The Reaction between 2,6-Lutidyllithium and 1-Chlorobut-3-ene.—The preparation of 2,6-lutidyllithium is a modification of the method reported[21] for 2-picolyllithium, and its reaction with the butenyl chloride is based upon the reaction[22] of 2-picolyllithium with isopropyl bromide. A freshly prepared solution of phenyllithium was added dropwise to a solution of 2,6-lutidine (25 ml) in ether (100 ml), and stirred for 1 hr. Chlorobutene (10 g) in ether (50 ml) was added slowly and the mixture was then heated under gentle reflux for 5 hr, cooled, and poured onto ice. The ether phase was separated and the aqueous phase was further extracted with ether. The bases were extracted into 1 *M* aqueous hydrochloric acid. The acid solution was basified with potassium hydroxide and was extracted with ether; the solution was dried ($MgSO_4$) and the ether was removed. Fractional distillation of the yellow oil gave 12.1 g (68%) of 1-[2-(6-methylpyridyl)]-pent-4-ene (**3**) as a colorless liquid: bp 104.5–105° (14 mm); $n^{20}D$ 1.5008; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 3098, 2948, 2860, 1640, 1590, 1580, 1460, 995, and 910 cm^{-1}; nmr, AB_2 absorption (τ 2.78, 3.16, J = 7 Hz) (3 H), complex absorptions centered at *ca.* τ 3.7 and 5.0 (3 H), a triplet (τ 7.3, J = 7 Hz) (2 H), a singlet (τ 7.5) (3 H), and four other aliphatic protons (τ 7.6–8.6).

Anal. Calcd for $C_{11}H_{15}N$: C, 82.1; H, 9.3; N, 8.7. Found: C, 82.0; H, 9.4; N, 8.9.

Bromination of the Olefin 3.—This reaction was performed several times in different solvents. The procedure used in each case was the same and only one experiment shall be reported.

Bromine (2.4 g) dissolved in dioxane (10 ml) was added dropwise to a stirred solution of olefin **3** (2.4 g) in dioxane (10 ml). When the reaction was complete, the solvent was evaporated under reduced pressure. The residual yellow paste was partitioned between water and chloroform to give an effective separation of the two products **6** and **4**. The relative yields of the two products could be estimated at this state from the ultraviolet absorptions of the two solutions. Solvents used (ratios of cyclized/uncyclized product) follow: carbon tetrachloride (0.19), dioxane (0.96), 2% aqueous dioxane (5.25). Evaporation of the combined chloroform extracts gave a yellow oil which was distilled to give 6-(4,5-dibromopentyl)-2-picoline (**4**) as a colorless liquid: bp 95–96° (0.01 mm); $n^{20}D$ 1.4640; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 3024, 2858, 1587, 1570, 1451, and 793 cm^{-1}; nmr, AB_2 absorption (τ 2.78 and 3.16, J = 7 Hz) (3 H), a triplet (τ 7.3 J = 7 Hz) (2 H), a singlet (τ 7.5) (3 H), a complex absorption (τ 5.5–6.5) (3 H), and a complex absorption at τ 7.6–8.5 (4 H); mass spectrum, base peak at m/e 106 and parent peaks at m/e 319, 321, and 323 (intensity ratios 1:2:1).

Anal. Calcd for $C_{11}H_{15}NBr_2$: C, 41.2; H, 4.7; N, 4.4; Br, 49.8. Found: C, 41.5; H, 5.1; N, 4.4; Br, 49.6.

(18) E. J. Witzemann, W. Lloyd-Evans, H. Hoss, and E. F. Schroeder, *Org. Syn.*, **11**, 26 (1931).

(19) H. Saikashi, Y. Taniguchi, and H. Ogawa, *Yakugaku Zasshi*, **82**, 1262 (1962); *Chem. Abstr.*, **58**, 1388c (1963).

(20) Melting points and boiling points are uncorrected. Microanalyses were performed by the Microanalytical Section, C. S. I. R. O., Melbourne, Australia, under the direction of Dr. K. W. Zimmerman and Mr. H. J. Jerie. Ultraviolet spectra were recorded in the solvent stated on a Shimadzu photoelectric spectrophotometer Model QR-50. All infrared spectra of solids were measured in potassium chloride disks and those of liquids were measured as liquid films between sodium chloride plates using a Perkin-Elmer Infracord spectrophotometer. Nmr spectra were obtained on a Varian Associates HR 60 spectrometer and were calibrated by the side-band technique. All measurements were made on AnalaR carbon tetrachloride solutions using tetramethylsilane as an internal reference, or on deuterium oxide solutions with acetone or sodium 3-(trimethylsilyl)-1-propane sulfonate as internal references. Mass spectra were measured on an Associated Electronic Industries MS9 spectrometer. When the term nitrogen is used, it should be taken to mean oxygen-free, dry nitrogen, and ether to mean anhydrous, peroxide-free ether.

(21) R. B. Woodward and E. C. Kornfeld, *Org. Syn.*, **29**, 44 (1949).

(22) L. Osuch and R. Levine, *J. Amer. Chem. Soc.*, **78**, 1723 (1950).

Concentration of the aqueous phase yielded **6** which, when crystallized from acetone and acetonitrile, gave white crystals: mp 243–244°; $\lambda_{max}^{H_2O}$ 275 mμ (log ε 3.8); ν_{max} 1620, 1610, 1490, 915, 855, 834, and 810 cm^{-1}; nmr, AB_2 absorption (τ 1.81 and 2.24, J = 7 Hz) (3 H), a broad triplet (τ 6.67, J = 7 Hz) (2 H), a singlet (τ 7.13) (3 H), and a complex absorption (τ 7.18–8.20) (4 H).

Anal. Calcd for $C_{11}H_{15}NB_2$: C, 41.2; H, 4.7; N, 4.4; Br, 49.8. Found: C, 41.1; H, 5.0; N, 4.2; Br, 50.0.

Attempted Cyclization of 6-(4,5-Dibromopentyl)-2-picoline (4).—Several attempts were made to cause dibromide **4** to cyclize. All reactions were studied by ultraviolet spectroscopy and thin layer chromatography (tlc). The following summarizes solvent, concentration (% v/v), temperature, and reaction time (hr): EtOH, 10, 40, 24; EtOH, 10, 78, 24; $HCON(Me_3)_2$, 10, 153, 12; $HOCH_2CH_2OH$, 10, 197, 12; nil, 100, 300, 24. In no case could evidence be found for the cyclized salt **6**.

Reaction between 7 and Sodium Cyanide.—To a solution of **6** (0.32 g) in water (5 ml) was added a solution of sodium cyanide (0.1 g) in water (0.5 ml). The solution was heated to 80° for 1 hr, cooled, and evaporated to 2 ml under reduced pressure. The tarry solid was removed and sodium perchlorate (0.4 g) in water (1 ml) was added. The crystals (46 mg, 15%) which separated were crystallized with difficulty from an acetone–ethanol–water mixture to give almost white crystals of 6-methyl-4-methylene-1,2,3,4-tetrahydroquinolizinium (**5**) perchlorate which decomposed explosively at *ca.* 220° without melting: $\lambda_{max}^{H_2O}$ 277 mμ (log ε 3.85); ν_{max} 3040, 2940, 1655, 1620, 1565, 1480, 1095, and 794 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}NClO_4$: Cl, 13.7. Found: Cl, 14.0.

The chloroplatinate as precipitated with sodium chloroplatinate. The flesh-colored crystals were recrystallized several times from water; the melting point (172–173°) was undepressed by admixture with sample prepared in a similar manner (81% yield) using sodium carbonate instead of sodium cyanide.

Anal. Calcd for $C_{22}H_{28}N_2PtCl_6$: C, 36.4; H, 3.9; Pt, 26.8. Found: C, 35.8; H, 4.0; Pt, 27.0.

Prins Reaction on 1-Chlorobut-3-ene.—As difficulty was experienced in trying to reproduce the yield reported in the literature[23] for the Prins reaction on allyl chloride, a modification of that procedure was followed.

Paraformaldehyde (160 g) was mixed with ether (200 ml) and the mixture was cooled in an ice bath. Fuming sulfuric acid (160 ml) was slowly added over a period of *at least* 4 hr. To the white slurry was added the olefin **2** (40 g) in ether (200 ml) over a period of 1 hr, and the mixture was then allowed to warm to room temperature. The reaction mixture was poured onto a vigorously stirred mixture of ice (750 g) and potassium carbonate (500 g) and stirred thoroughly for 30 min. The mixture was filtered and the residue was washed with ether. The aqueous phase was extracted with ether and the ether extracts were combined and dried ($MgSO_4$). The solvent was removed (12 mm) and the residue was distilled rapidly (0.1 mm) into a cooled receiver. The yellow distillate was shaken with anhydrous potassium carbonate, filtered, and fractionally distilled to yield 49 g (71%) of 4-(2-chloroethyl)-,13-dioxane (**10**): bp 43–44° (0.5 mm); n^{20}D 1.4444; ν_{max} 1305, 1282, 1250, 1151, 1040, 847, and 829 cm^{-1}.

Anal. Calcd for $C_6H_{11}ClO_2$: C, 47.9; H, 7.4; Cl, 23.6. Found: C, 48.0; H, 7.5; Cl, 23.4.

Preparation of 6-{3-[4-(1,3-Dioxanyl)propyl]}-2-picoline (12).—The procedure was similar to the reaction between 2,6-lutidyllithium and 1-chlorobut-3-ene and the product was a colorless oil (64% yield): bp 111–112° (0.5 mm); n^{20}D 1.5173; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 2940, 2860, 1590, 1580, 1452, 1152, 1120, 1039, and 792 cm^{-1}; nmr, AB_2 absorption (τ 2.78 and 3.18, J = 7 Hz) (3 H), AB quartet (τ 5.05 and 5.37, J = 6 Hz) (2 H), a complex absorption from τ 5.9 to 6.8 (3 H), a triplet at τ 7.25 (J = 7 Hz) (2 H), a singlet at τ 7.5 (3 H), and a complex absorption from τ 7.9 to 8.8 (6 H).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.6; H, 8.7; N, 6.3. Found: C, 70.5; H, 8.6; N, 6.2.

Cleavage of the 1,3-Dioxane 12.—Lithium iodide (2.5 g) was dissolved in acetic anhydride and boron trifluoride etherate (3.5 ml) was added. To this solution was added the 1,3-dioxane (0.4 g) and the mixture was stirred for 15 min. The mixture was poured onto a slurry of ice (100 g) and potassium carbonate (60 g) and the product was continuously ether extracted. The ether extracts were evaporated and the residue was dried by azeotropic distillation with benzene. The brown viscous oil was chromatographed over B. D. H. silica gel with chloroform. The eluate was collected in 20-ml fractions and fractions 8–60 and 75–125 were combined to yield **11** and **14**, respectively. The solvent was continuously changed to 5% methanol to elute the glycol **13** in fractions 170–210.

The combined fractions (8–60) were evaporated free of chloroform and separated from the small amount of colorless impurity by molecular distillation (10^{-4} mm) giving 80 mg (15%) of colorless viscous oil, 6-(4,6-diacetoxyhexyl)-2-picoline (**11**): n^{20}D 1.4620; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 2968, 2939, 1738, 1460, 1273, and 1250 cm^{-1}; nmr, AB_2 absorption (τ *ca.* 2.6 and 3.15, J = *ca.* 7.5 Hz) (3 H), a triplet (τ 7.32, J = 7 Hz) (2 H), a singlet (τ 7.56) (3 H), two singlets (τ 8.03 and 8.05) (6 H), a triplet (τ 5.93, J = 7 Hz) (2 H), a quintet (τ 5.00, J = 6 Hz) (1 H), and a complex absorption (6 H) between τ 7.5 and 8.5.

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.5; H, 7.9; N, 4.8. Found: C, 65.6; H, 7.8; N, 4.8.

By the same procedure fractions 75–125 yielded 180 mg (40%) of 6-(6-acetoxy-4-hydroxyhexyl)-2-picoline (**14**): n^{20}D 1.4310; λ_{max}^{EtOH} 266 and 277 mμ (log ε 3.5 and 3.4); ν_{max} 3430, 2966, 2937, 1730, 1460, 1270, and 1242 cm^{-1}; nmr contained a triplet (τ 5.93) (2 H) and a quintet (τ 6.43) (1 H).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.9; H, 8.4; N, 5.6. Found: C, 66.7; H, 8.2; N, 5.3.

Fractions 170–210 were combined and evaporated free from solvent. The resultant viscous yellow oil was rechromatographed over B. D. H. alumina with 10% methanol in chloroform. From the eluate was recovered 20 mg (5%) of almost colorless 2-(4,6-dihydroxyhexyl)-6-methylpyridine (**13**): n^{20}D 1.3788; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 3340, 2925, 1593, 1582, 1540, 1100, 1063, and 830 cm^{-1}; nmr, AB_2 pattern (τ 2.6 and 3.15, J = 7 Hz) (3 H), a broad singlet (τ 5.5) (2 H), a quintet (τ 6.12, J = 6 Hz) overlapping a triplet (τ 6.31, J = 6 Hz) (3 H), a triplet (τ 7.22, J = 7 Hz) (2 H), a singlet (τ 7.55) (3 H), and a complex absorption centered at τ *ca.* 8.5 (6 H); mass spectrum, m/e (% of base peak) 91 (20), 107 (100), 120 (38), 134 (22), 162 (34), 164 (45), 191 (20), and 209 (12).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.9; H, 9.1; N, 6.7. Found: C, 68.4; H, 8.9; N, 6.3.

Treatment of Hydroxyacetate 14 with Phosphorus Tribromide.—The reaction was carried out in dimethoxyethane with phosphorus tribromide at 85° for 1 hr. The mixture was neutralized with aqueous bicarbonate, the solvent was removed under vacuum and the residue repeatedly triturated with benzene. The product was subjected to repeated preparative scale tlc over Merck alumina using 20% carbon tetrachloride in chloroform, to yield 45 mg (16%) of a pale yellow viscous oil, 6-(6-acetoxy-4-bromohexyl)-2-methylpyridine (**15**): n^{20}D 1.5201; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 2970, 2942, 2868, 1737, 1593, 1580, 1462, and 1265 cm^{-1}; nmr, AB_2 pattern (τ 2.6 and 3.15, J = 7 Hz) (3 H), a triplet (τ 5.95, J = 7 Hz) (2 H), a poorly resolved quintet (τ 6.45, J = *ca.* 5 Hz) (1 H), a triplet (τ 7.2, J = 7 Hz) (2 H), a singlet (τ 7.56) (3 H), and a complex absorption centered at τ 8.4 (6 H).

Anal. Calcd for $C_{14}H_{20}BrNO_2$: C, 53.5; H, 6.4. Found: C, 53.0; H, 6.3.

Hydrolysis of 6-(6-Acetoxy-4-bromohexyl)-2-methylpyridine.—The bromide **15** was dissolved in 50% aqueous dioxane and was rapidly hydrolyzed on adding silver perchlorate. After filtration and thorough extraction with benzene, the product was isolated by preparative scale tlc and was identical with the hydroxyacetate **15**.

Preparation of 4-[6-(2-Picolyl)]butyraldehyde Acetal (16).—The method of preparation was identical with those described above. The product (63%) was a colorless liquid: bp 80–80.5° (0.01 mm); ν_{max} 3076, 2966, 2900, 1590, 1579, 1453, 1370, 1130, 1063, and 800 cm^{-1}; nmr, AB_2 pattern (τ 2.6 and 3.15, J = 7 Hz) (3 H), a triplet (τ 5.58, J = 5 Hz) (1 H), a complex symmetrial absorption centered around τ 6.58 (4 H), a triplet (τ 7.30, J = 7 Hz) (2 H), a singlet (τ 7.57) (3 H), a complex absorption around τ 8.4 (4 H), and a triplet (τ 8.84, J = 7 Hz) (6 H).

Hydrolysis of the Acetal 16.—Generally the hydrolysis was performed on the crude acetal from the above reaction. Fractional distillation of the product gave a colorless liquid (80%): bp 95–96° (1.5 mm); n^{20}D 1.5117; λ_{max}^{EtOH} 266 and 272 mμ (log ε 3.5 and 3.4); ν_{max} 3030, 2840, 2770, 1720, 1588, 1576, 1450, 1150,

(23) C. Price and I. Krishnamurti, *J. Amer. Chem. Soc.*, **72**, 5335 (1950).

1043, 992, and 310 cm^{-1}. The chloroplatinate crystallized from water, mp 184–185° dec.

Anal. Calcd for $C_{20}H_{26}Cl_6N_2O_2Pt$: C, 32.8; H, 3.6; Pt, 26.6. Found: C, 32.2; H, 4.0; Pt, 26.7.

Preparation of 6-(5-Carbethoxypent-4-enyl)-2-picoline (19).—The aldehyde **17** and phosphorane, in equimolar amounts, were heated in refluxing ethanol for 6 hr. After removal of the solvent, and drying of the residue by azeotropic distillation with benzene, petroleum ether (40–60°) was added to the viscous residue causing triphenylphosphine oxide to precipitate. After removal of the precipitate and the solvent, a honey-colored oil (84%) remained. Chromatography over B. D. H. silica gel with chloroform gave a pale yellow oil (62%) which was sufficiently pure for most purposes. An analytical sample was obtained by molecular distillation (10^{-4} mm): $n^{20}D$ 1.5211; λ_{max}^{EtOH} 210, 266, and 272 mμ (log ε 4.1, 3.5, and 3.4).

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.1; H, 8.2; N, 6.0. Found: C, 72.2; H, 8.0; N, 6.2.

Bromination of the α,β-Unsaturated Ester 19.—The ester **19** (0.34 g) was dissolved in water (5 ml) by adding dioxane (*ca.* 10 ml). To the vigorously stirred solution was added bromine (0.25 g) in dioxane (5 ml) over a period of 5 min. After stirring for 0.5 hr, the solvent and excess bromine were removed under vacuum. The impure crystals were triturated with chloroform and filtered to yield a buff-colored product (0.46 g, 88%), mp 128–130°. Recrystallization from acetonitrile and from acetone gave an analytical sample of 6-methyl-4-carbethoxybromomethyl-1,2,3,4-tetrahydroquinolizinium bromide (**20**) as white crystals: mp 132–132.5°; $\lambda_{max}^{H_2O}$ 275 mμ (log ε 3.8); ν_{max} 2960, 2906, 2840, 1615, 1582, 1489, 1302, 1257, 1212, 1030, and 802 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}Br_2NO_2$: C, 42.7; H, 4.9; N, 3.6; Br, 40.6. Found: C, 42.9; H, 5.1; N, 3.8; Br, 40.8.

The perchlorate precipitated from aqueous solution and could be crystallized from water. It decomposed explosively at *ca.* 180° without melting: $\lambda_{max}^{H_2O}$ 275 mμ (log ε 3.8); ν_{max} 2962, 2907, 2842, 1516, 1583, 1490, 1306, 1090, 1030, and 800 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}BrClNO_6$: N, 3.4. Found: N, 3.4.

The chloroform extracts were chromatographed over B. D. H silica gel and purified by molecular distillation (10^{-4} mm) to give a pale pink oil. A mass spectral determination gave the following data: *m/e* (% of base peak) 395 (1), 393 (2), 391 (1), 315 (5), 311 (5), 268 (3), 233 (16), 120 (10), and 107 (100).

Treatment of 20 with Base.—Several combinations of base and solvent were studied, but the results were always the same.

The salt **20** (100 mg) was dissolved in water (1.5 ml) and to this was added dropwise a solution of potassium carbonate (50 mg) in water (2 ml). At the end of the addition an oil separated. The product was extracted with carbon tetrachloride, the solvent was removed, and the product was dried by azeotropic distillation with benzene. The product was obtained as a pale yellow oil (50 mg, 63%) after chromatography over B. D. H. silica gel with carbon tetrachloride: nmr, olefinic and aromatic protons (τ 2.5–3.5) (4 H), a quartet (τ 5.86, J = 7 Hz) (2 H), a triplet (τ 7.3, J = 7 Hz) (2 H), a singlet (τ 7.5) (3 H), a complex multiplet (τ 7.5–8.4) (4 H), and a triplet (τ 8.7, J = 7 Hz); mass spectrum, *m/e* (% of base peak), 107 (100), 108 (32), 120 (18), 158 (10), 230 (32), 231 (9), 311 (12), and 313 (12).

Anal. Calcd for $C_{14}H_{18}BrNO_2$: C, 53.9; H, 5.8; Br, 25.6; N, 4.5. Found: C, 53.7; H, 5.6; Br, 25.2; N, 4.5.

Registry No.—**3**, 15981-94-9; **4**, 15981-95-0; **5** perchlorate, 15982-08-8; **5** chloroplatinate, 12244-22-3; **6** bromide, 15981-96-1; **10**, 15981-97-2; **11**, 15981-98-3; **12**, 15982-00-0; **13**, 15982-01-1; **14**, 15982-02-2; **15**, 15981-99-4; **16**, 15982-03-3; **17** chloroplatinate, 12244-21-2; **19**, 15982-04-4; **20** bromide, 15982-05-5; **20** perchlorate, 15982-06-6; **21**, 15982-07-7.

Acknowledgments.—The author is extremely grateful to Professor L. M. Jackman (Pennsylvania State University) and Dr. Q. N. Porter (Melbourne) for patient advice and stimulating discussion. Acknowledgment is also made to the Dunlop Rubber Co. and G. J. Coles Pty. Ltd. (Australia) for financial assistance.

Reaction of Aziridine and Oxirane Derivatives with Diphenyliodonium Iodide[1,2]

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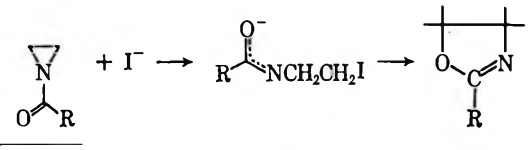
The reaction of diphenyliodonium iodide with suitably substituted 2-benzoylaziridines affords 2,5-diaryloxazoles and the corresponding α,β-unsaturated ketone. The removal of the nitrogen atom and the subsequent formation of the corresponding olefin is found to be a general phenomenon. The mechanism proposed for the deamination involves coordination of diphenyliodonium iodide with the unshared electrons of the carbonyl oxygen followed by proton loss and subsequent elimination. The formation of the substituted 2,5-diaryloxazole proceeds by carbon–carbon cleavage of the aziridine ring to produce an intermediate tight ion pair. The reaction between diphenyliodonium iodide and α,β-epoxy ketones causes a major fragmentation of the oxide ring and affords a mixture of aryl acids and ketones.

1-Aroylaziridines are known to be readily isomerized into 2-aryl-Δ^2-oxazolines by the action of aluminum halides, heat, or nucleophilic reagents.[4–11] These rearrangements are formally analogous to the vinylcyclopropane–cyclopentene isomerization and the details of the transformation have been elegantly elucidated by Heine and coworkers.[11] The isomerization by nucleophilic reagents has been explained by a reaction scheme involving attack by a nucleophile, such as iodide ion, on one of the carbon atoms of the aziridine ring to form a 2-iodoethylamine anion (eq 1). In a subsequent step the ion cyclizes to the oxazoline and regenerates the iodide ion. Substituted 1-acyl-2-alkylaziridines also undergo pyrolytic isomerization to form N-allylamides.[12,13] Kinetic and stereochemical



(1)

(1) Support of this research by a grant from the National Institute of Health (Grant GM-13990-01) is acknowledged with appreciation.

(2) For a preliminary report of this work, see A. Padwa and L. Hamilton, *Tetrahedron Lett.*, 1861 (1967).

(3) National Institute of Health Predoctoral Fellow, 1964–1967.

(4) H. Heine and Z. Proctor, *J. Org. Chem.*, **23**, 1554 (1958).

(5) H. Heine, M. E. Fetter, and E. Nicholson, *J. Amer. Chem. Soc.*, **81**, 2202 (1959).

(6) H. Heine, W. G. Kenyon, and E. M. Johnson, *ibid.*, **83**, 2570 (1961).

(7) P. Thrum and A. R. Day, *J. Med. Chem.*, **8**, 107 (1965).

(8) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 3828 (1965).

(9) P. E. Fanta and E. N. Walsh, *J. Org. Chem.*, **30**, 3574 (1965).

(10) P. E. Fanta and E. N. Walsh, *ibid.*, **31**, 59 (1966).

(11) H. Heine, *Angew. Chem. Intern. Ed. Engl.*, **1**, 528 (1962).

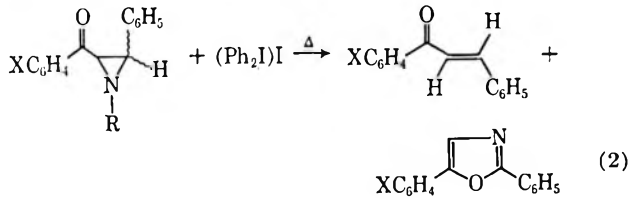
(12) P. E. Fanta, "Heterocyclic Compounds with Three and Four Membered Rings," part I, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 524–575.

(13) P. E. Fanta and M. K. Kathan, *J. Heterocycl. Chem.*, **1**, 293 (1964).

investigations suggest that the rearrangement is an intramolecular, concerted *cis* elimination involving transfer of a proton from the alkyl group to the amido oxygen.[13] The successful application of these reactions to the related 2-aroylaziridine system has not been reported in the literature.[2] In view of the close structural relationship between these two sets of compounds, it became of interest to determine whether similar processes would occur with 2-aroylaziridines. The present paper describes a novel diphenyliodonium iodide catalyzed rearrangement of suitably substituted 2-benzoylaziridines to form 2,5-diaryloxazoles and the corresponding α,β-unsaturated ketone. Extension of this reaction into the related oxirane system resulted in a major fragmentation of the oxide ring.

When the reaction of *trans*-1-benzyl-2-phenyl-3-benzoylaziridine (I) and sodium iodide was carried out using anhydrous acetone, there was obtained a complex mixture of products. Thin layer chromatography of the crude reaction mixture suggested the presence of between eight and ten products. Numerous attempts to induce a ring expansion of a variety of other *cis*- and *trans*-arylaroylaziridines with sodium iodide afforded only brown, tarry materials which defied all attempts at characterization. Thus *cis*-1-cyclohexyl-2-phenyl-3-*p*-toluylaziridine (VIII) with sodium or potassium iodide in ether, acetone, or dioxane produced only recovered starting material and brown tars. Similar results were obtained in acetone or tetrahydrofuran solutions containing potassium thiocyanate as the nucleophilic reagent. Since 1-aroylaziridines are isomerized by Lewis acids, it was felt that a mild electrophilic species, such as diphenyliodonium iodide, may effect the desired transformation.

Treatment of *trans*-1-benzyl-2-phenyl-3-benzoylaziridine (I) with an equivalent amount of diphenyliodonium iodide in refluxing tetrahydrofuran resulted in the complete disappearance of starting material. The products were separated by liquid–liquid partition chromatography and purified by crystallization. The products of the reaction were *trans*-benzalacetophenone (73%), 2,5-diphenyloxazole (7%), and iodobenzene (83%). Structures of the products (eq 2) follow from



(2)

their spectral properties and by comparison with authentic samples. Under the same reaction conditions described above, but without diphenyliodonium iodide, only recovered aziridine I was obtained. On the other hand, refluxing a toluene solution of I in the presence or absence of diphenyliodonium iodide afforded only brown tarry material. When diphenyliodonium iodide was heated to reflux in toluene, a high yield of iodobenzene (70%) was obtained after 6 hr.[14] This observation indicates that in a high boiling solvent, such as toluene, the decomposition of diphenyliodonium iodide to iodobenzene proceeds at a rate faster than reaction with the arylaroylaziridine. It must be concluded that diphenyliodonium iodide is involved in the reaction with arylaroylaziridines prior to its decomposition. This was demonstrated by heating a solution of I and iodobenzene in tetrahydrofuran and recovering starting aziridine in better than 98% yield. Thereafter, tetrahydrofuran was used as solvent so as to retard the decomposition of diphenyliodonium iodide and to promote its reaction with the arylaroylaziridine.

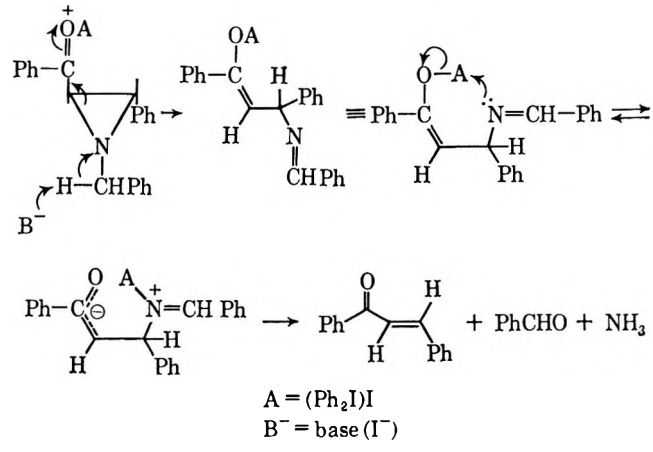
The removal of the nitrogen atom and the subsequent formation of the corresponding olefin in the reaction between an arylaroylaziridine and diphenyliodonium iodide is found to be a general phenomenon. Table I summarizes data on the products obtained

TABLE I
REACTIONS OF ARYLAROYLAZIRIDINES WITH DIPHENYLIODONIUM IODIDE

Compd	Substituents	Yield of oxazole, %	Yield of substituted *trans*-benzalacetophenone, %
I	X = H; R = $CH_2C_6H_5$ (*trans*)	7	73
II	X = H; R = $CH_2C_6H_5$ (*cis*)	8	75
III	X = H; R = C_6H_{11} (*trans*)		76
IV	X = H; R = C_6H_{11} (*cis*)		72
V	X = CH_3; R = $CH_2C_6H_5$ (*trans*)	44	52
VI	X = CH_3; R = $CH_2C_6H_5$ (*cis*)	41	54
VII	X = CH_3; R = C_6H_{11} (*trans*)		67
VIII	X = CH_3; R = C_6H_{11} (*cis*)		65

with a number of substituted *cis,trans*-arylaroylaziridines. The isolation of an α,β-unsaturated ketone from the reaction mixture suggest that the reaction proceeds by coordination of diphenyliodonium iodide with the unshared electrons of the carbonyl oxygen followed by proton loss and subsequent elimination, as formulated in Scheme I. Support for the

SCHEME I

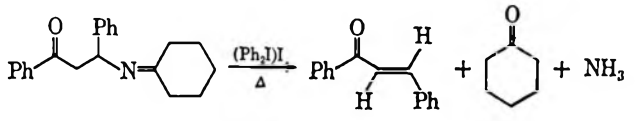


above contention was found in the observation that 1-cyclohexyl-2-phenyl-3-benzoylaziridine (III) gave *trans*-benzalacetophenone and cyclohexanone in comparable yields. Similarly, *trans*-1-benzyl-2-*p*-toluyl-3-phenylaziridine (V) afforded benzaldehyde and ammonia. Further confirming evidence for the above mechanism was obtained by the finding that an authentic sample of N-1-(2-benzoyl-1-phenylethyl)cyclohexanimine[15] was converted rapidly and quantita-

(14) F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler, and C. C. Lumpkin, *J. Amer. Chem. Soc.*, **75**, 2708 (1953).

(15) A. Padwa and L. Hamilton, *ibid.*, **89**, 102 (1967).

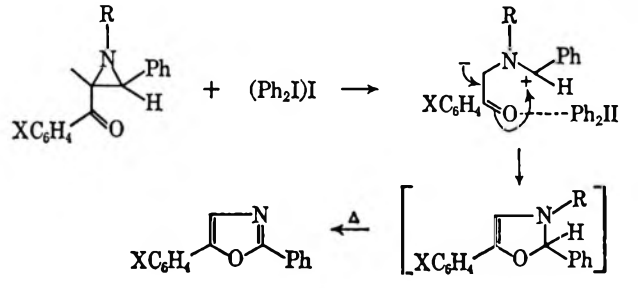
tively into *trans*-benzalacetophenone and cyclohexanone when subjected to the reaction conditions[16] (eq 3).



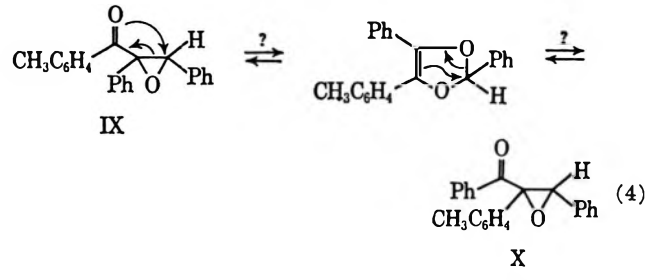
(3)

One possible sequence of steps to explain the diphenyliodonium iodide catalyzed transformation of arylaroylaziridines to diaryloxazoles involves coordination of diphenyliodonium iodide with the carbonyl group (Scheme II). Such coordination can induce cleavage of the carbon–carbon bond of the strained aziridine ring. Subsequent ring closure to a 2,3-dihydrooxazole followed by oxidation readily accounts for the observed product. The possibility that the 2,3-dihydrooxazole was formed by an iodide ion catalyzed isomerization, as suggested by Heine for the rearrangement of N-aroylaziridines to Δ^2-oxazolines, was discounted by the observation that the yield of diaryloxazole did not increase when sodium iodide was added to the reaction mixture. Interestingly, the yield of diaryloxazole is much higher with aziridines V and VI than with aziridines I and II. A reasonable explanation is that a considerable amount of positive character appears on the carbonyl oxygen in the transition state for rearrangement. This is compatible with the above mechanism if it is assumed that diphenyliodonium iodide behaves as a weak Lewis acid and by coordinating with the carbonyl oxygen promotes ring cleavage. This, in turn, is strongly supported by the fact that other Lewis acids, such as $ZnCl_2$ or $AlBr_3$, can also promote the rearrangement to 2,5-diaryloxazoles. Alternatively, it may be argued that an ion-pair mechanism may be in operation, with carbon–oxygen bond formation preceding carbon–carbon bond breakage.

SCHEME II

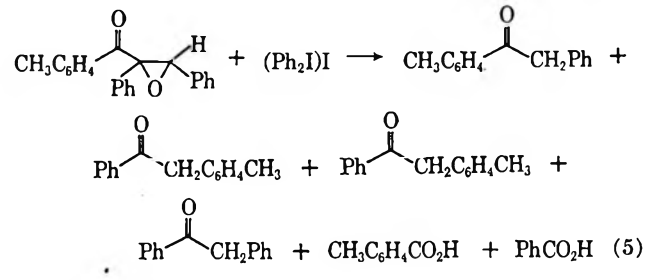


It is noteworthy that in the reaction of aziridines I and V, toluene is formed as a by-product. The fact that N-cyclohexylaziridines III and VII afford only α,β-unsaturated ketones suggests that the initial 2,3-dihydrooxazole may either undergo further oxidation or revert back to starting material. In the N-cyclohexyl system, the 2,3-dihydrooxazole would be expected to be resistant toward further oxidation. A similar reversal has been reported in the related oxazoline system.[17] These observations plus the knowledge that cyclopropyl carboxyaldehyde has been found to be in equilibrium with dihydrofuran at high temperatures[18] suggested that a reaction sequence could be designed which would involve a diphenyliodonium iodide catalyzed expansion of an α,β-epoxy ketone to a substituted 1,3-dioxolene. Once formed, the five-membered ring could revert back to an α,β-epoxy ketone in either of two directions. In order to test for this possibility, we investigated the possible conversion of IX into X (eq 4). The technique chosen to follow the



(4)

proposed rearrangement involved nmr analysis of the reaction mixture. Treatment of IX with diphenyliodonium iodide at 240° for 30 min resulted in the complete disappearance of the resonance associated with the epoxide proton (τ 5.50). The nmr spectrum of the crude reaction mixture had a new, one-proton singlet at τ 5.78 and a broad three-proton signal at 7.68. Careful scrutiny by vapor phase chromatography, however, failed to reveal the presence of X. Chromatography of the mixture on a silica gel column afforded 4-methyldesoxybenzoin (18%), 4′-methyldesoxybenzoin (2%), desoxybenzoin (30%), *p*-toluic acid (32%), and benzoic acid (18%) (see eq 5).



(5)

Furthermore, the only reaction observed between diphenyliodonium iodide and other suitably substituted α,β-epoxy ketones was fragmentation of the oxide ring and the formation of a mixture of aryl acids and ketones. The results are displayed in Table II and details are given in the Experimental Section. The foregoing data are taken to imply that ring expansion of α,β-epoxy ketones does not occur in the presence of either diphenyliodonium iodide or other Lewis acids.

The conversion of α,β-epoxy ketones into a mixture of aryl ketones and acids requires a major fragmentation of the oxide ring. This result may be rationalized by a number of different routes shown in Scheme III. One possibility (route A) involves the acid- (Lewis) catalyzed migration of an aroyl group to produce a β-diketone, which under work-up conditions affords the observed products.[19] The fact that 1,2-diphenyl-1,3-

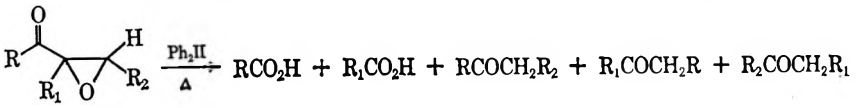
(16) The fact that the imine undergoes an elimination does not necessarily exclude an initial coordination of the Lewis acid with the nitrogen atom as a significant mechanistic process.

(17) H. L. Wehrmeister, *J. Org. Chem.*, **30**, 664 (1965).

(18) C. L. Wilson, *J. Amer. Chem. Soc.*, **69**, 3002 (1947).

(19) The preferential migration of an aroyl group is not without precedent. See, for example, J. D. Roberts, D. R. Smith, and C. C. Lee, *ibid.*, **73**, 618 (1951); H. O. House and D. J. Reif, *ibid.*, **77**, 6525 (1955).

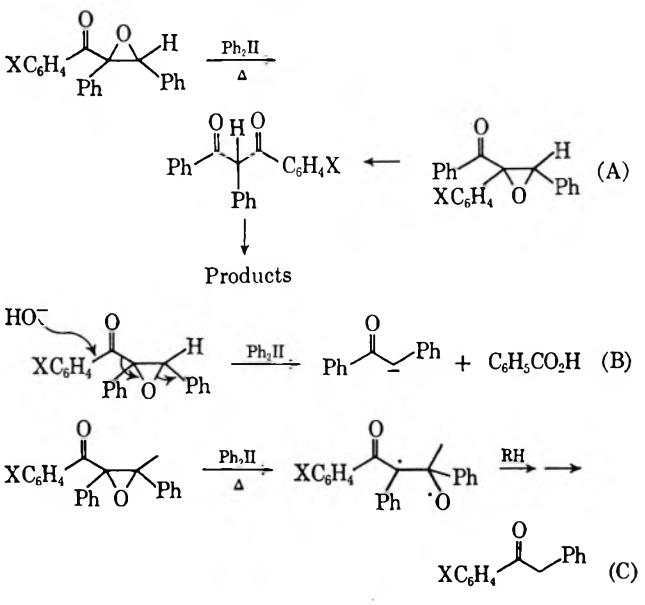
TABLE II
REACTION OF SUBSTITUTED EPOXY KETONES WITH DIPHENYLIODONIUM IODIDE[a]



Substituents (starting epoxide)	% yield RCO2H	R1CO2H	RCOCH2R2	R1COCH2R	R2COCH2R1
R = C6H4CH3; R1 = R2 = C6H5 (IX)	32	18	18	...	30
R = R2 = C6H5; R1 = C6H4CH3 (X)	36	14	12	10	27
R = R1 = C6H5; R2 = C6H4CH3 (XI)	49	...	46	4	...
R = CH3; R1 = R2 = C6H5 (XII)[b]	24	24	15	...	33
R = R2 = C6H5; R1 = CH3 (XIII)[c]	35	15	19	17	11

[a] All reactions were carried out in sealed tubes at 240° for 30 min. [b] Prepared by the procedure described by H. E. Zimmerman, L. Singer, and B. S. Thyagarajan [*J. Amer. Chem. Soc.*, **81**, 108 (1959)]. [c] Prepared by the procedure described by H. O. House and D. J. Reif [*ibid.*, **77**, 6525 (1955)].

SCHEME III



butanedione (XIV) gives the same products as does XII and XIII when exposed to similar experimental conditions adds credence to this proposition. However, if this were the only available route, one would expect epoxy ketones IX and X (or XII and XIII) to give an identical product distribution. Experimentally (Table II), reaction of XII afforded a mixture of aryl ketones substantially different from that obtained from XIII. Thus it seems that the migration of an aroyl group in the diphenyliodonium iodide reaction of an α,β-epoxy ketone only provides for a partial explanation of the observed results. Another mechanistic possibility (route B) involves attack of a nucleophile on the carbon atom of the aroyl group with concomitant ring opening. The basic hydrolysis of 2-cyclohexyl-3-phenyl-3-benzoyloxazirane bears similar characteristics and provides ample precedent for this route.[20] Route C involves cleavage of the carbon–oxygen bond of the epoxide ring followed by hydrogen abstraction and β scission. These explanations can not be differentiated by product analysis and consequently it is not possible to choose among them. The relative importance of each route seems to depend on the particular system involved. In fact, it is quite probable that all three routes may be occurring to a varying degree at the same time.

(20) A. Padwa, *J. Amer. Chem. Soc.*, **87**, 4365 (1965).

Experimental Section[21]

Reaction of 1-Benzyl-2-*p*-toluyl-3-phenylaziridine (V) with Diphenyliodonium Iodide in Tetrahydrofuran.—A mixture of 0.50 g of *trans*-aziridine (V) and 0.62 g of diphenyliodonium iodide in 200 ml of tetrahydrofuran was heated to reflux for 72 hr. Thin layer chromatography demonstrated the complete disappearance of starting material and the appearance of three major new spots. Removal of the solvent *in vacuo* left a red oil which was subjected to liquid–liquid column chromatography. The chromatogram showed three well-resolved peaks with retention volumes of 1800 2400, and 2800 ml. The first fraction (0.37 g, 60%) was shown to be pure iodobenzene by comparison of its infrared spectrum with that of an authentic sample. The second peak in the chromatogram (0.15 g, 44%) was a colorless oil which solidified upon standing. Recrystallization from 95% ethanol gave white crystals, mp 81–82°. Comparison of the nmr, uv, and ir spectra of this species with an authentic sample of 2-phenyl-5-*p*-tolyloxazole established its identity. The mixture melting point of these two materials was undepressed at 81–82°. The last fraction in the chromatogram (0.17 g, 52%) was shown to be pure *trans*-4-methylbenzalacetophenone by comparison with an authentic sample. The crude reaction mixture was also analyzed by vpc. The analytical gas chromatography was performed on an Aerograph 350-B instrument with helium as the carrier gas on a column of Carbowax (20% on Chromosorb W) at 90°. Comparison of retention times and infrared spectra with those of known samples of toluene and benzaldehyde established the identity of the products. By employing benzonitrile as a suitable internal standard, a 40% yield of benzaldehyde and a 43% yield of toluene were found. Identical results were obtained when *cis*-1-benzyl-2-*p*-toluyl-3-phenylaziridine was treated with diphenyliodonium iodide in refluxing tetrahydrofuran.

Treatment of 1-Benzyl-2-benzoyl-3-phenylaziridine with Diphenyliodonium Iodide in Tetrahydrofuran.—A mixture of 0.63 g of *trans*-aziridine I and 0.82 g of diphenyliodonium iodide in 200 ml of tetrahydrofuran was refluxed for 72 hr. The solvent was removed by distillation and the dark yellow oil was chromatographed on a liquid–liquid partition column. The chromatogram consisted of three well-defined peaks with retention volumes of 1800, 2200, and 2680 ml. The first peak (0.51 g, 63%) was shown to be pure iodobenzene by comparison with an authentic sample. The second peak (45 mg) was identified as 2,5-diphenyloxazole. The last peak (310 mg) was shown to be *trans*-benzalacetophenone. Careful examination of the crude reaction mixture by vapor phase chromatography showed two additional compounds. The analytical gas chromatography was performed on a Aerograph A-90 instrument with helium as the carrier gas on a Carbowax column (20% on Chromosorb W) at 90°. Collection of these compounds and comparison with authentic samples of toluene and benzaldehyde established their identity. Comparable results were obtained when *cis*-1-benzyl-2-benzoyl-3-phenyl-

(21) All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark, and Alfred Bernhardt Laboratories, Hohenweg, Germany. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 60 Mc with the Varian Associates high-resolution spectrophotometer. Tetramethylsilane was used as an internal standard.

aziridine was treated with diphenyliodonium iodide in refluxing tetrahydrofuran.

Reaction of 1-Cyclohexyl-2-benzoyl-3-phenylaziridine with Diphenyliodonium Iodide in Tetrahydrofuran.—A mixture of 0.61 g of *cis*-1-cyclohexyl-2-benzoyl-3-phenylaziridine (IV) and 0.82 g of diphenyliodonium iodide in 200 ml of tetrahydrofuran was allowed to reflux for 68 hr. The solvent was removed *in vacuo* to leave a dark yellow oil which was subjected to liquid–liquid partition chromatography. The chromatogram showed two major peaks with retention volumes of 1800 and 2700 ml of mobile phase. The first peak (518 mg, 64%) was identified as iodobenzene. The second peak (316 mg, 76%) was shown to be *trans*-benzalacetophenone. There was no detectable quantities of 2,5-diphenyloxazole found in the reaction mixture. Examination of the crude reaction mixture by vapor phase chromatography showed the presence of cyclohexanone (69%). The analytical gas chromatography was performed on an Aerograph A-90 instrument employing a Carbowax column (20% on Chromosorb W) at 50°. Similar results were obtained when *trans*-1-cyclohexyl-2-benzoyl-3-phenylaziridine was treated with diphenyliodonium iodide in refluxing tetrahydrofuran.

Treatment of 1-Cyclohexyl-2-*p*-toluyl-3-phenylaziridine with Diphenyliodonium Iodide in Tetrahydrofuran.—A mixture of 0.64 g of *cis*-1-cyclohexyl-2-*p*-toluyl-3-phenylaziridine (VIII) and 0.82 g of diphenyliodonium iodide in 200 ml of tetrahydrofuran was allowed to reflux for 76 hr. Evaporation of the solvent afforded a dark yellow oil which was subjected to liquid–liquid partition chromatography. The optical density trace showed two peaks with retention volumes of 1800 and 2800 ml of mobile phase. The first peak consisted of 496 mg (61%) of iodobenzene. The second peak contained 286 mg (67%) of *trans*-4-methylbenzalacetophenone. There was no detectable quantities of 2-phenyl-5-*p*-tolyloxazole found in the reation mixture. Analysis of the crude reaction mixture by gas chromatography confirmed the presence of cyclohexanone (59%). The analytical gas chromatography was performed on an Aerograph A-90 instrument using a SE-30 silicon column (20% on Chromosorb W) at 70°.

Decomposition of N-1-(2-Benzoyl-1-phenylethyl)cyclohexanimine with Diphenyliodonium Iodide.—N-1-(2-Benzoyl-1-phenylethyl)cyclohexanimine was prepared according to the procedure of Padwa and Hamilton.[16] A mixture of 0.31 g of N-1-(2-benzoyl-1-phenylethyl)cyclohexanimine and 0.41 g of diphenyliodonium iodide in 50 ml of tetrahydrofuran was allowed to reflux for 18 hr. The solvent was removed *in vacuo*, and the crude residue was analyzed by vapor phase chromatography on an Aerograph A-90 instrument. The products were separated on a column of Dow 710 silicone oil (0.2% on glass beads) at 170° at a flow rate of 50 cc/min. The material of retention time 6.2 min was collected in a Dry Ice trap connected to the gas outlet. The material obtained had an infrared spectrum and retention time identical with that of an authentic sample of *trans*-benzalacetophenone (78%). Analysis of the crude reaction mixture at 50° showed a major component with retention time of 2.3 min. Comparison of retention time and infrared spectra with that of an authentic sample of cyclohexanone established its identity. A sufficient quantity of water is present in the solvent to effect the conversion of the imine into ammonia and the carbonyl compound.

Preparation of α,β-Diphenyl-4-methylacrylophenone Oxide (IX).—A mixture of 59 g of benzyl-*p*-tolyl ketone and 40 g of benzaldehyde was saturated with hydrogen chloride gas at 0°. The solution was kept overnight and the solid material which formed was collected by filtration, washed thoroughly with 95% ethanol and ether, and dried to yield 100 g of 1-(4-methylphenyl)-2,3-diphenyl-3-chloro-propan-1-one. The chloride could be dehydrohalogenated to α,β-diphenyl-4-methylacrylophenone by refluxing a mixture of 60 g of the chloride, 40 g of fused sodium acetate, and 15.7 g of sodium carbonate in 240 ml of methanol for 3 hr. The solid which precipitated was collected by filtration, washed thoroughly with water, and dried to yield 55 g of α,β-diphenyl-4-methylacrylophenone. Recrystallization from ethanol gave a white crystalline solid, mp 105–106°. The infrared spectrum of the crystalline compound (KBr) is characterized by a carbonyl band at 6.06 μ. The nmr spectrum showed a singlet at τ 7.68 and a multiplet centered at 2.60. The peak areas were in the ratio of 1:5.

A solution of 30 g of the unsaturated ketone in 600 ml of methanol was treated with 60 ml of 30% hydrogen peroxide and 30 ml of 6 *N* aqueous sodium hydroxide. After the mixture had been stirred for 20 hr at room temperature, it was poured into 2 l. of water and extracted with ether. The ether extract was washed with water and dried over magnesium sulfate; the ether was removed. The residual α,β-diphenyl-4-methylacrylophenone oxide crystallized from 95% ethanol as white plates, mp 103–104°, to yield 17 g (60%). The infrared spectrum of this material showed a strong carbonyl band at 5.97 μ. The nmr spectrum showed a multiplet at τ 2.40 and singlets at 5.50 and 7.68. The peak areas were in the ratio of 14:1:3.

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.07; H, 5.73. Found: C, 83.89; H, 5.73.

Preparation of α-Tolyl-β-phenylacrylophenone Oxide (X).—The procedure of Kohler and Nygard was adapted to the present case.[22] A mixture of 15 g of 4′-methyldesoxybenzoin and 9.2 g of benzaldehyde was saturated with hydrogen chloride gas at 0° and was allowed to stand overnight at room temperature. The resulting solid was washed with 95% ethanol and dried to yield 18 g of β-chlorobenzal-4′-methyldesoxybenzoin. A solution of 10 g of the chloride, 7.0 g of fused potassium acetate, and 2.3 g of anhydrous sodium carbonate in 50 ml of methanol was boiled under reflux for 3 hr. The solid which precipitated was washed with water and collected by filtration to yield 6.8 g of α-tolyl-β-phenylacrylophenone. Recrystallization from ethanol gave crystals, mp 123–124°. The infrared spectrum (KBr) had a carbonyl band at 6.05 μ. The nmr spectrum in deuteriochloroform exhibited a multiplet centered at τ 2.40 and a singlet at 7.70.

A mixture of 5.0 g of α-tolyl-β-phenylacrylophenone, 20 ml of 30% hydrogen peroxide, 8.0 ml of 6 *N* sodium hydroxide, and 250 ml of methanol was stirred for 24 hr at room temperature. After the reaction mixture had been poured into water, the precipitated solid was recrystallized from 95% ethanol, mp 73–74°. The infrared spectrum exhibited a carbonyl band at 5.95 μ. The nmr spectrum consisted of a multiplet centered at τ 2.50 (14 H), a singlet at 5.50 (1 H), and a singlet at 7.92 (3 H).

Anal. Calcd for $C_{24}H_{18}O_2$: C, 84.08; H, 5.73. Found: C, 84.02; H, 5.83.

Preparation of α-Phenyl-β-tolylacrylophenone Oxide (XI).—Dry hydrogen chloride gas was passed through an ice-cooled mixture of 40 g of desoxybenzoin and 24 g of *p*-tolylaldehyde for 5 hr. The mixture was allowed to stand at room temperature for an additional 8 hr. The resulting solid was thoroughly washed with 95% ethanol and dried to yield 77 g of 1,2-diphenyl-3-*p*-tolyl-3-chloro-propan-1-one. The crude chloride could be dehydrohalogenated by refluxing a solution of 60 g of the chloride, 40 g of fused potassium acetate, and 16 g of anhydrous sodium carbonate in 250 ml of methanol for 48 hr. The solid which precipitated was collected by filtration, washed with water, and recrystallized once from 95% ethanol. The crude α-phenyl-β-tolylacrylophenone was used without further purification. A mixture of 5.0 g of the unsaturated ketone, 20 ml of 30% hydrogen peroxide, 8.0 ml of 6 *N* sodium hydroxide, and 250 ml of methanol was stirred for 48 hr at room temperature. After the reaction mixture had been poured onto water, the precipitated solid was recrystallized from 95% ethanol, mp 129–130°. The infrared spectrum exhibited a carbonyl band at 5.95 μ. The nmr consisted of a multiplet centered at τ 2.50 (14 H), a singlet at 5.50 (1 H), and a singlet at 8.80 (3 H).

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.08; H, 5.73. Found: C, 83.75; H, 5.76.

General Procedure for the Reaction of Substituted Acrylophenone Oxides with Diphenyliodonium Iodide.—All the reactions described were run under essentially the same experimental conditions and are illustrated by the following experiment with α,β-diphenyl-4-methylacrylophenone oxide (IX). A mixture of 0.5 g of IX and 0.5 g of diphenyliodonium iodide was heated in a sealed tube at 240° for 30 min. The resulting mixture was extracted with ether and the ethereal extracts were washed with 5% sodium bicarbonate solution and then with water. After the organic layer had been dried over sodium sulfate, the ether was removed and the impure material, dissolved in benzene, was chromatographed on a 2.5 × 91 cm column of silica gel, slurry packed in 3:1 benzene–hexane. The column was eluted with 9:1 benzene–hexane (2 l.) followed by benzene (1 l.). The eluent, in 50-ml fractions, was concentrated and dried *in vacuo*. The crystalline solid from elution with 9:1 benzene–hexane was identified as desoxybenzoin and that obtained from pure benzene was shown to be 4′-methyldesoxybenzoin.

(22) E. P. Kohler and E. M. Nygard, *J. Amer. Chem. Soc.*, **52**, 4128 (1930).

The crude reaction mixture was also analyzed by vpc. The analytical gas chromatography was performed on a F & M Model 5720 instrument with helium as the carrier gas on a Carbowax 20M column (20% on Chromosorb P) at 240°. Comparison of retention times and infrared spectra with those of the authentic ketone and acid established the identity of the products. The results are recorded in Table II.

Registry No.—I, 6476-12-6; II, 6372-57-2; III, 2211-61-2; IV, 2211-65-6; V, 6476-13-7; VI, 6372-58-3; VII, 6372-29-8; VIII, 6476-39-7; IX, 15830-93-0; X, 15830-81-6; XI, 15856-59-4; XII, 15830-82-7; XIII, 15856-60-7; α,β-diphenyl-4-methylacrylophenone, 15830-83-8; α-tolyl-β-phenylacrylophenone, 15830-84-9; diphenyliodonium iodide, 2217-79-0; N-1-(2-benzoyl-1-phenylethyl)cyclohexanimine, 14802-27-8.

Acknowledgment.—The authors are indebted to the U. S. Public Health Service (Grant GM 13990-01) for generous support of this research.

Small Charged Rings. XI.[1] Synthesis and Reactions of 1,1,2,2-Tetrasubstituted Azetidinium Salts[2]

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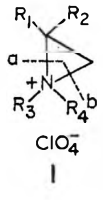
A convenient synthesis of 1,1,2,2-tetramethylazetidinium perchlorate (**2**) and 1-benzyl-1,2,2-trimethylazetidinium perchlorate (**3**) has been developed. The cyclization step in the sequence leading to these compounds involved treatment of γ-*sec*-aminoalkyl chlorides with silver perchlorate to afford the corresponding tertiary azetidine perchlorates in excellent yield. These were subsequently alkylated to give the quaternary azetidinium salts. 1,1-Dibenzyl-2,2-dimethylazetidinium perchlorate (**4**), as an intermediate, was found to undergo a facile eliminative ring opening in the presence of amines and could not be isolated. The structures of **2** and **3** have been verified by molecular weight determination and nmr spectroscopy. The tetramethyl salt **2** proved to be relatively unreactive, but the benzyltrimethyl salt **3** underwent solvolytic ring opening with alcohols to form N-(3-alkoxy-3-methylbutyl)-N-methylbenzylamine perchlorates. In the presence of sodium methoxide or upon heating in solution, both azetidinium salts exhibited a strong tendency to undergo eliminative ring opening to afford substituted 3-methyl-3-buten-1-ylamines. Azetidinium salt **3** combined with nitrones, specifically with substituted Δ¹-pyrroline-1-oxides, to afford 1:1 adducts containing the 2-oxa-1-aza-6-azoniabicyclo[5.3.0]decane ring system. This reaction is representative of a new type of ring expansion, expressed as ④⁺ + 3 → ⑦⁺, in which a four-membered charged ring combines with a 1,3-dipolar moiety to form a seven-membered charged ring. The structures of the adducts were established by cleavage of the 6,7 bond with lithium aluminum hydride, followed by cleavage of the 1,2 bond with zinc and acetic acid, accompanied by spectroscopic and chemical identification of the ultimate degradation products.

In the course of a continuing study of the reactions of 1,1,2,2-tetrasubstituted aziridinium salts (**1**), a



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number of facile ring openings and ring expansions have been observed.[4] In general, weak nucleophiles bring about ring opening at a so that SN1-type products are obtained,[5,6] while strong nucleophiles tend to approach the ring from the less hindered side in an SN2 manner to effect bond breaking at b.[7,8] Preliminary cleavage at a is also postulated as the initial step in the expansion of the aziridinium ring with aldehydes,[8] ketones,[9] and nitriles.[10] When both the 2 and the 3 position on the aziridinium ring are unsubstituted, more vigorous conditions are necessary for reaction to occur with nitriles.[11] These ring expansion reactions of aziridinium salts are codified within the general category ③⁺ + 2 → ⑤⁺, in which a charged, three-membered cycle is increased in size to a charged, five-membered cycle. The reaction of aziridinium salts with nitrones has introduced a new category: ③⁺ + 3 → ⑥⁺.[1] As a logical extension of this study, it was of interest to determine whether suitably substituted azetidinium rings could open and expand in a manner analogous to that of the more highly strained aziridinium system. Although a variety of azetidinium salts have been known for some time,[12,13] no extensive investigations into the chemistry of these charged four-membered heterocycles have been made until recently.[14-19]

(1) For the preceding article in this series, see N. J. Leonard, D. A. Durand, and F. Uchimaru, *J. Org. Chem.*, **32**, 3607 (1967).

(2) We are pleased to acknowledge the support of the National Science Foundation by Research Grant GP 2012.

(3) Lubrizol Corp. Fellow, 1964–1965; National Science Foundation Fellow, 1965–1967.

(4) For pertinent references and a general summary of work in this area, see N. J. Leonard, *Rec. Chem. Progr.*, **26**, 211 (1965).

(5) N. J. Leonard and K. Jann, *J. Amer. Chem. Soc.*, **84**, 4806 (1962).

(6) N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.*, **28**, 1499 (1963).

(7) J. V. Paukstelis, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1964.

(8) N. J. Leonard, E. F. Kiefer, and L. E. Brady, *J. Org. Chem.*, **28**, 2850 (1963).

(9) N. J. Leonard, J. V. Paukstelis, and L. E. Brady, *ibid.*, **29**, 3383 (1964).

(10) N. J. Leonard and L. E. Brady, *ibid.*, **30**, 817 (1965).

(11) E. Pfeil and U. Harder, *Angew. Chem.*, **77**, 505 (1965).

(12) S. A. Ballard and D. S. Melstrom in "Heterocyclic Compounds," Vol I, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p 78.

(13) J. A. Moore in "The Chemistry of Heterocyclic Compounds," Vol. XIX, part 2, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 885.

(14) A. Ebnöther and E. Jucker, *Helv. Chim. Acta*, **47**, 745 (1964).

(15) D. H. Wadsworth and O. E. Schupp, *J. Heterocycl. Chem.*, **3**, 230 (1966).

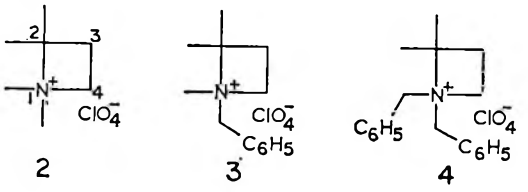
(16) G. Fodor, *J. Amer. Chem. Soc.*, **88**, 1040 (1966).

(17) (a) V. R. Gaertner, *Tetrahedron Lett.*, 343 (1967); (b) V. R. Gaertner, *J. Org. Chem.*, **32**, 2972 (1967).

(18) W. B. Wheatley and L. C. Cheney, *J. Amer. Chem. Soc.*, **74**, 1359 (1952).

(19) M. T. Wills, *Dissertation Abstr.*, **27B**, 423 (1966).

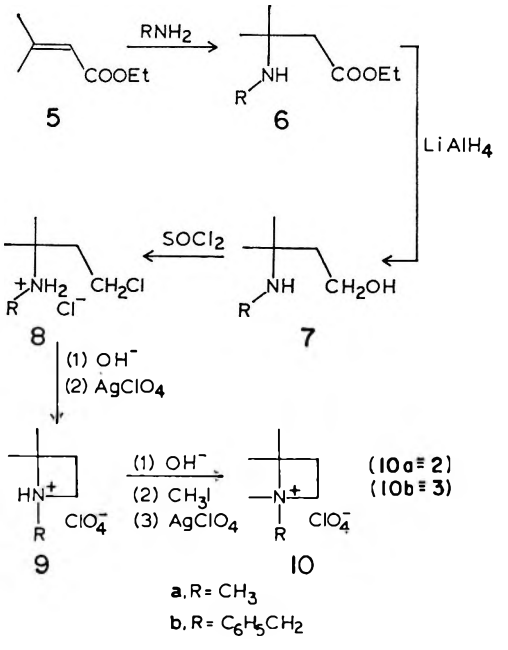
Our initial plan was to synthesize the azetidinium salts **2**–**4** and to study their reactions. It was anticipated that *gem*-dimethyl substitution at the 2 position would not only make ring formation from an acyclic precursor very efficient,[20,21] but would provide a tertiary carbon capable of carrying a developing positive charge, so that the azetidinium ring could open in an SN1 manner by cleavage of the 1,2 bond. Moreover, the selection of a series with progressively increasing benzyl substitution was directed by the finding that N-benzyl substitution greatly enhances the reactivity of aziridinium rings,[22] so much so that a 1,1-dibenzyl-2,2-dialkylaziridinium salt has not been isolated to date, and by the consideration that the series **2**–**4** would furnish a reasonably broad spectrum of reactivity.



2 **3** **4**

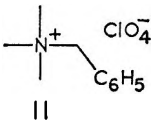
1,1,2,2-Tetramethylazetidinium perchlorate (**2**)[23] and 1-benzyl-1,2,2-trimethylazetidinium perchlorate (**3**) were synthesized conveniently and in good yield by way of the sequence shown in Scheme I. The conversion of

Scheme I



γ-chloroalkylamine salts **8** into azetidine salts **9** is the novel feature of this sequence. Treatment of **8** with aqueous base liberated the corresponding free amino chloride, which was isolated without purification. Cyclization to **9** was then effected by means of silver perchlorate at room temperature in either acetone or acetonitrile. Although the reaction proceeded slowly (silver chloride precipitated continuously for at least one day), the yields of **9** were excellent [quantitative for 1,2,2-trimethylazetidine perchlorate (**9a**) and 85% for 1-benzyl-2,2-dimethylazetidine perchlorate (**9b**)]. Work-up was relatively simple since the perchlorates could be separated from residual silver salts by extraction with methylene chloride. This facile reaction between γ-*sec*-aminoalkyl chlorides and silver perchlorate represents a new and useful route to the azetidine ring system,[24] assisted in these examples by the presence of the *gem*-dimethyl substitution. The azetidine salts **9a** and **9b** could be converted readily into azetidinium salts **2** and **3**, respectively, by methylation of the corresponding free 1,2,2-trisubstituted azetidines.

It was desirable to demonstrate that we were in fact dealing with four-membered rings and not eight-membered dimeric structures. Therefore, the molecular weight of **3** was determined in acetone. Since the extent of dissociation of **3** varied with its concentration in solution, it was necessary to obtain apparent molecular weight data at several concentrations and to compare this dissociative behavior with that of a model compound, benzyltrimethylammonium perchlorate (**11**). The data indicated that **3** consists of a singly



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charged cation and anion, as opposed to the doubly charged cation and two singly charged anions required by the dimeric structure (See Experimental Section for details.) Further confirmation of the four-membered ring structures of **2** and **3** was obtained from the nmr spectra of these salts in trifluoroacetic acid. It had been noted previously[25] that α-methylene protons in azetidinium salts are deshielded to an unusual extent. The spectrum of the tetramethyl salt **2** exhibited a triplet at τ 5.83 ppm for the CH_2–N^+ protons. The chemical shift was in contrast to those observed for the α-methylene protons in aziridinium salts (τ 6.7–7.1)[5,6,24] and in pyrrolidinium and piperidinium salts (τ 6.4–6.6). The nmr spectrum of the benzyltrimethyl salt **3** was particularly interesting in that the chemical shifts of the nonequivalent α-methylene protons differed by approximately 1 ppm (τ 5.1–5.7 and 6.1–6.6, both multiplets) owing to the anisotropy of the aromatic ring.[26] The β-methylene protons were apparently undifferentiated by this anisotropy.

Whereas 1-benzyl-2,2-dimethylazetidine (**12**) could be methylated readily to form the azetidinium salt **3**, efforts to benzylate **12** to form 1,1-dibenzyl-2,2-di-

(20) W. R. Vaughan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward [*J. Org. Chem.*, **26**, 138 (1961)] applying Grob's stereoelectronic requirements for fragmentation [C. A. Grob, *Experientia*, **13**, 126 (1957); C. A. Grob, "Kekule Symposium, Theoretical Organic Chemistry," Butterworth and Co. Ltd., London, 1959, pp 114–127] have suggested that one of the most favorable situations for effective cyclization to the azetidine system will be found in a 3-aminopropyl system in which there is *gem* disubstitution on C-3 and no substitution on C-1 and C-2.

(21) For a general discussion of the *gem*-dimethyl effect, see (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley and Sons, Inc., New York, N. Y., 1965, pp 191–192; (b) N. L. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960), and references therein.

(22) P. C. Kelley, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1965.

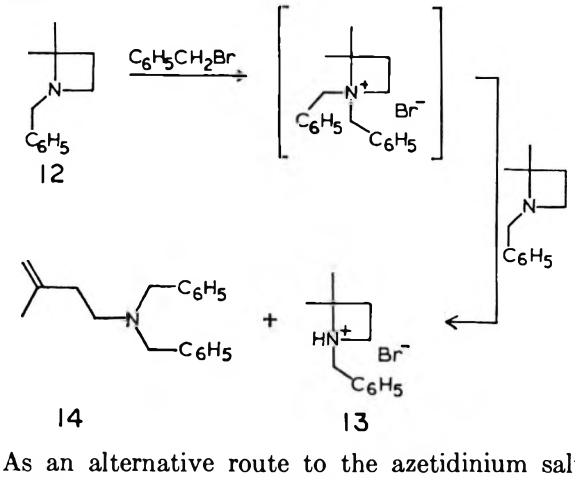
(23) 1,1,2,2-Tetramethylazetidinium reineckate has been prepared previously; see C. A. Grob, F. Ostermayer, and W. Raudenbusch, *Helv. Chim. Acta*, **45**, 1672 (1962).

(24) A similar method has been employed in the synthesis of aziridinium salts; see N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **30**, 821 (1965).

(25) O. E. Edwards, G. Fodor, and L. Marion, *Can. J. Chem.*, **44**, 13 (1966).

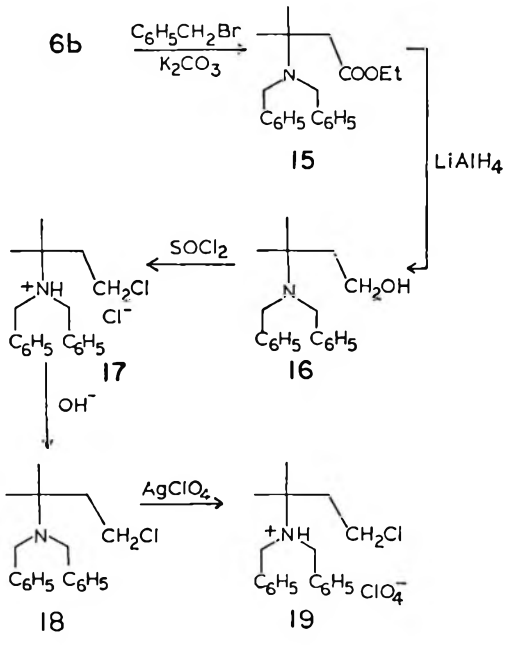
(26) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 18.

methylazetidinium perchlorate (**4**) were unsuccessful. In all attempts, following treatment of the crude benzylation product mixture with silver perchlorate, the only salt that could be isolated was 1-benzyl-2,2-dimethylazetidine perchlorate (**9b**), the conjugate acid of **12**. The fact that **9b** was always isolated in low yield led us to suspect that the desired dibenzylazetidinium salt was acting as a proton source. This was shown to be the case when the azetidine **12** was treated with benzyl bromide in the absence of solvent. Addition of ether to the crude reaction mixture caused the precipitation of 1-benzyl-2,2-dimethylazetidine hydrobromide (**13**) in 42% yield. Work-up of the resulting ethereal filtrate afforded a free amine which exhibited nmr signals in deuteriochloroform at τ 2.72 (multiplet, 10 H) and 6.45 (singlet, 4 H), indicative of a dibenzylamino group, and at 5.35 (apparent singlet, 2 H) and 8.43 (singlet, 3 H), suggesting the presence of the moiety $CH_3—C{=}CH_2$. The structure assigned to the amine was thus N-(3-methyl-3-buten-1-yl)dibenzylamine (**14**). It therefore appears that azetidine **12** is alkylated by benzyl bromide to form 1,1-dibenzyl-2,2-dimethylazetidinium bromide, but that this material is unstable under the reaction conditions and reacts with additional **12** in the manner of a base-promoted Hofmann elimination to afford a 1:1 mixture of azetidine salt **13** and amino olefin **14**. The ease with which this proton abstraction occurred is somewhat surprising and merits discussion in greater detail (see below).



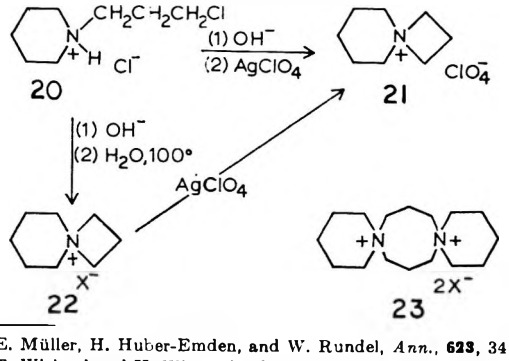
As an alternative route to the azetidinium salt **4**, we investigated the possibility of cyclizing N-(4-chloro-2-methyl-2-butyl)dibenzylamine (**18**) with silver perchlorate. The synthesis of **18** was accomplished according to the sequence shown in Scheme II. Treatment of **18** with silver perchlorate in acetone resulted in a slow precipitation of silver chloride over a 2-day period. Following the usual work-up procedure, a perchlorate salt (**19**) was isolated in very low yield. This material exhibited an nmr spectrum similar to that which would be expected for the dibenzylazetidinium salt, but the infrared spectrum showed a band for N^+–H at 3080 cm.$^{-1}$ Microanalysis indicated that **19** was merely N-(4-chloro-2-methyl-2-butyl)dibenzylamine perchlorate. Although no attempt was made in this case to detect the presence of the amino olefin **14** in the reaction mixture, the formation of **19** in low yield suggested that, as in the attempted benzylations of azetidine **12**, the azetidinium salt was formed, but quickly underwent a Hofmann elimination in the presence of excess amine. Variations in both rate and order of reagent addition were found to be ineffective in suppressing this ring-opening reaction.

SCHEME II



In view of the apparent lability of 1,1-dibenzyl-2,2-dimethylazetidinium perchlorate (**4**) toward amines, it was concluded that further attempts to prepare and isolate this compound should avoid the presence of any basic material. One such attempt, based upon the known reaction of amine salts with diazomethane,[27-29] was the synthesis of **4** directly from 1-benzyl-2,2-dimethylazetidine perchlorate (**9b**). Treatment of **9b** in acetonitrile with diazomethane at 0° afforded 1-benzyl-1,2,2-trimethylazetidinium perchlorate (**3**), albeit in moderate yield. However, treatment of **9b** in acetonitrile with phenyldiazomethane under a variety of conditions, including the presence of boron trifluoride etherate as a catalyst, failed to yield any N,N-dibenzyl product (**4**).

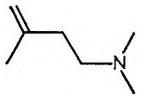
Silver perchlorate,[24] used as a cyclizing reagent in the conversion of **8** (as the base) into **9**, may also be applied to γ-*t*-aminoalkyl chlorides, so that quaternary azetidinium salts are obtained directly. For example, treatment of the γ-chloroalkylamine salt **20** with aqueous base liberated the corresponding free amine, which was cyclized with silver perchlorate in acetone to afford 4-azoniaspiro[3.5]nonane perchlorate (**21**) in 48% yield.



(27) E. Müller, H. Huber-Emden, and W. Rundel, *Ann.*, **623**, 34 (1959).
(28) T. Wieland and H. Wiegandt, *Chem. Ber.*, **93**, 1167 (1960).
(29) R. Daniels and C. G. Kormendy, *J. Org. Chem.*, **27**, 1860 (1962).

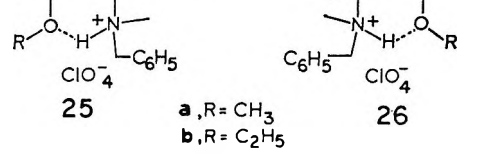
The fact that the yield was only moderate in this case is very likely due to the absence of *gem*-dialkyl groups which would facilitate the cyclization.[21] Evidence for the presence of the four-membered ring in **21** was obtained from the nmr spectrum (in deuterium oxide), which exhibited a four-proton triplet at τ 5.32 for the azetidinium CH_2–N^+ protons. Since the ring system present in **21** is identical with that of the first postulated azetidinium salt,[30] 4-azoniaspiro[3.5]nonane bromide (**22**, X = Br), an opportunity was provided to determine whether the early workers had actually synthesized an azetidinium ring, or whether the vigorous conditions that were employed favored formation of the corresponding eight-membered dimer,[31] 6,10-diazoniadispiro[5.3.5.3]octadecane dibromide (**23**, X = Br). To this end, **20** was treated with aqueous base to liberate the free amino chloride, which was subsequently heated with water at 100°. Work-up afforded the quaternary chloride as a syrup. A picrate prepared from this material had a melting point identical with that reported earlier.[30] Treatment of the syrup with silver perchlorate yielded a perchlorate salt that was identical with **21** in all respects. The quaternary chloride therefore had structure **22** (X = Cl), 4-azoniaspiro[3.5]nonane chloride, and the original claim of azetidinium salt formation was shown to be correct.

Having devised an efficient synthesis for two (**2** and **3**) of the three azetidinium salts initially desired, we proceeded to investigate the chemistry of these salts in some detail. 1,1,2,2-Tetramethylazetidinium perchlorate (**2**) proved to be completely unreactive toward reagents that have been shown to bring about facile solvolytic ring opening or ring expansion of representative aziridinium salts. For example, no detectable reaction occurred upon treatment of **2** with refluxing methanol for 35 hr, or with refluxing acetone for 5 days. The four-membered ring also failed to open under conditions of catalytic hydrogenolysis. However, **2** was found to undergo reaction with sodium methoxide in methanol. The major product exhibited nmr signals in deuteriochloroform at τ 5.28 (apparent singlet, 2 H) and 8.26 (singlet, 3 H) indicative of the CH_3—C=CH_2 grouping, thus permitting the structure to be assigned as N-(3-methyl-3-buten-1-yl)dimethylamine (**24**). No signal ascribable to the methoxy moiety could be detected, indicating that eliminative ring opening was the main reaction. It will be recalled that a similar Hofmann elimination took place during attempts to prepare 1,1-dibenzyl-2,2-dimethylazetidinium perchlorate (**4**), although the base involved in that case (*i.e.*, a free amine) was much weaker than sodium methoxide.

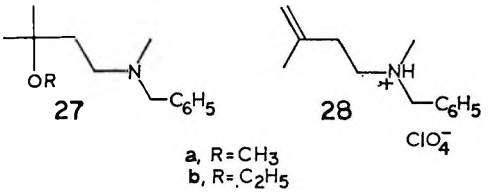


24

In contrast to the lack of reactivity of **2** in solvolytic ring opening, the four-membered ring in 1-benzyl-1,2,2-trimethylazetidinium perchlorate (**3**) was opened readily, reflecting the electron-withdrawing influence and, to some extent, the steric effect of the benzyl group. Upon treatment with refluxing methanol, compound **3** was converted slowly into a two-component mixture. The major product, isolated by fractional crystallization, displayed an infrared band at 3070 cm^{-1} for N^+–H and had an elemental composition satisfactory for $C_{14}H_{24}ClNO_5$, indicating that **3** had combined with methanol in a 1:1 manner. The nmr spectrum of this material in trifluoroacetic acid exhibited signals for $ArCH_2$–N^+H (τ 5.60, doublet), CH_3–N^+H (τ 6.96, doublet), and CH_3–O (τ 6.65, singlet). A clear distinction between the isomeric structures **25a** and **26a** was not offered, however, since a two-proton multiplet at τ 6.2–6.7 could be ascribed to either CH_2–N^+ (in **25a**) or CH_2O (in **26a**). The nmr spectrum (in deuteriochloroform) of the amine mixture liberated from the crude methanolysis product was more definitive. The presence of signals for CH_3–O (τ 6.93, singlet) and CH_2–N (τ 7.4–7.8, multiplet) together with the absence of any signal corresponding to CH_2–O (*i.e.*, at lower field than CH_3–O) was indicative of structure **27a**. The azetidinium ring had therefore opened in an Sn1 manner to afford **25a**, N-(3-methoxy-3-methylbutyl)-N-methylbenzylamine perchlorate. Evidence for the cyclic hydrogen-bonded configuration as drawn in **25a** was provided by the nmr spectrum which displayed two signals (τ 8.65 and 8.85) for $(CH_3)_2C$–O indicating that the methyl groups were nonequivalent. In the spectrum of **27a**, where no hydrogen bonding is possible, there was only one signal (τ 8.92) for these groups. The identification of the minor product of the methanolysis as N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine perchlorate (**28**) will be discussed shortly.



25 **a**, R = CH_3 **b**, R = C_2H_5 **26**



27 **28**

a, R = CH_3 **b**, R = C_2H_5

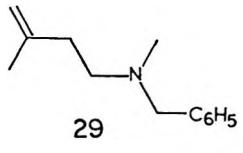
Since the methanolysis of analogous aziridinium salts is generally complete after 2 hr at reflux temperature,[5,7] it was of interest to determine the rate of opening of the azetidinium ring under similar conditions. The reaction between azetidinium salt **3** and methanol was therefore followed by means of nmr spectroscopy; pertinent details regarding the procedure are given in the Experimental Section. The data showed that the reaction is essentially complete after 8 hr and that the initial rate of formation of the amino ether **25a** is approximately three times the initial rate of formation of the amino olefin salt **28**.

In an analogous manner, azetidinium salt **3** reacted in refluxing ethanol to give a mixture of N-(3-ethoxy-3-methylbutyl)-N-methylbenzylamine perchlorate (**25b**) and the amino olefin salt **28**. The nmr spectrum of **25b** in deuteriochloroform displayed signals for $ArCH_2$–N^+H (τ 5.57, doublet), CH_3–N^+H (τ 7.01, doublet),

(30) S. Gabriel and R. Stelzner, *Ber.*, **29**, 2381 (1896).
(31) H. Hörlein and R. Kneisel, *ibid.*, **39**, 1429 (1906).

CH_2–N^+ (τ 6.4–6.9, multiplet), and CH_2–O (τ 6.61, quartet). Upon conversion of perchlorate **25b** into the corresponding free amine (**27b**), new signals appeared for $ArCH_2$–N (τ 6.51, singlet), CH_3–N (τ 7.81, singlet), CH_2–N (τ 7.3–7.7, multiplet), and CH_2–O (τ 6.67, quartet). Integration of the spectrum showed that the last signal corresponded to two protons, confirming the absence of an additional CH_2–O grouping and firmly establishing the assigned structure **27b** (and thus **25b** as well). The presence of hydrogen bonding in **25b** was demonstrated by the fact that the nmr spectrum of this salt exhibited two signals (τ 8.80 and 8.96) for $(CH_3)_2C$–O, whereas only one signal (τ 8.86) for this moiety appeared in the spectrum of **27b**. Though formation of the amino olefin salt **28** occurred to a greater extent in this case than during methanol treatment of **3**, formation of the amino ether was still the major reaction.

It was considered that treatment of the benzyltrimethylazetidinium salt **3** with sodium methoxide might open the ring in an SN2 manner, since methoxide is a much stronger nucleophile than methanol. However, the free amine that was actually obtained from this reaction proved to be N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine (**29**), as evidenced by nmr signals at τ 5.34 (apparent singlet, 2 H) and 8.32 (singlet, 3 H) for the CH_3—C=CH_2 moiety, as well as the lack of any signal attributable to CH_3—O.

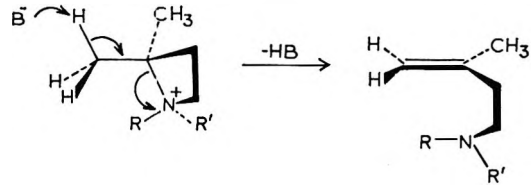


29

Attempts to effect a ④$^+$ + 2 → ⑥$^+$ ring expansion of azetidinium salt **3** by reaction with acetone or acetonitrile were likewise unsuccessful. In both instances, the only product that could be obtained was identified as **28**, the same amino olefin perchlorate that was formed as a by-product in the alcoholyses of **3**. This material was characterized by the nmr signals shown (in deuteriochloroform) at τ 5.61 (doublet, 2 H) and 7.07 (doublet, 3 H) for $ArCH_2$—N^+H and CH_3—N^+H, respectively, as well as at τ 5.20 (apparent singlet, 2 H) and 8.32 (singlet, 3 H) for the CH_3—C=CH_2 grouping. Infrared absorption at 3070 for N^+—H and at 1650 and 905 cm^{-1} for C=CH_2 supported this structural assignment.

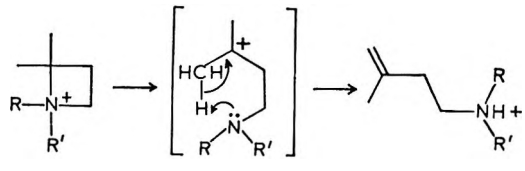
It is appropriate at this point to consider the reasons behind the relative ease with which azetidinium salts **2**, **3**, and **4** undergo eliminative ring opening. Two types of elimination have been observed for these compounds, namely based-promoted (*cf.* the attempted preparations of the dibenzyldimethyl salt **4**, and the reactions of the tetramethyl salt **2** and the benzyltrimethyl salt **3** with sodium methoxide) and "thermal" (*cf.* the alcoholyses and attempted ring expansions of **3**). In both types, the only amino olefin that could be detected was that obtained by loss of a hydrogen from one of the *gem*-dimethyl groups. It has been found that treatment of azetidinium salt **3** with sodium iodide in refluxing acetone also results in such an elimination. The facility with which the base-promoted eliminations occur can be explained relatively easily. In the normal transition state leading to Hofmann elimination, the quaternary nitrogen, the α and β carbons, and the β hydrogen all lie in a *trans* coplanar arrangement.[32] Upon examination of Dreiding models of our azetidinium salts, it can be seen that such an arrangement involving any of the six hydrogens on the *gem*-dimethyl groups is readily achieved. This property, together with the strain inherent in the four-membered ring, apparently serves to lower the free energy of activation to such an extent that elimination is the predominant if not exclusive reaction, provided that a base is present to accept the β hydrogen. The proposed mechanism for the base-promoted elimination is shown in Scheme III. It is more difficult to rationalize the ease with

SCHEME III



which the so-called "thermal" eliminations occur. A concerted mechanism is unlikely in this case since the perchlorate anion is not sufficiently basic to facilitate removal of the β hydrogen. A more plausible explanation is that the amino olefin is formed *via* the same ring-opened intermediate that gives rise to solvolysis product; this mechanism is shown in Scheme IV. There are,

SCHEME IV

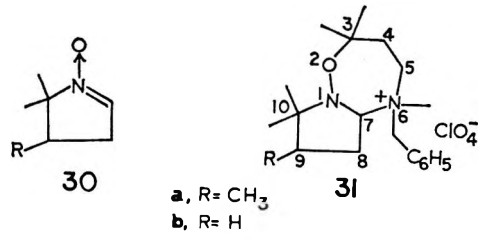


however, several discrepancies associated with this mechanism. If a carbonium intermediate such as that shown is actually formed, it would be expected that some ring-expanded product would be obtained when acetone or acetonitrile is present. In addition, some of the thermodynamically more stable olefin would very likely be formed. The products may be explained by kinetic control. Thus, alcohols, which are more nucleophilic than acetone or acetonitrile, are more effective than the latter two in attacking the intermediate before any rearrangement can take place. Moreover, rearrangement to give the less substituted olefin is kinetically favored owing to the six-membered geometry of the transition state shown in Scheme IV. The above considerations are admittedly speculative, and further study is necessary to elucidate more fully the mechanism of this "thermal" type of elimination. For example, there remains the possibility that the solvent (*i.e.*, alcohol, acetone, or acetonitrile) is acting as a proton-transfer agent in these reactions.

Although 1-benzyl-1,2,2-trimethylazetidinium perchloroate (**3**) failed to undergo ring expansion with either acetone or acetonitrile, expansion of this azetidinium ring could be effected by reaction with nitrones, in particular 4,5,5-trimethyl-Δ^1-pyrroline-1-oxide (**30a**)

(32) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, N. Y., 1959, p 484.

and 5,5-dimethyl-Δ^1-pyrroline-1-oxide (**30b**).[33] When an intimate mixture of azetidinium salt **3** and either nitrone was allowed to stand at room temperature for more than a week followed by a short period of heating at 60°, a product having the correct analysis for a 1:1 adduct was isolated in moderate yield. These adducts were tentatively assigned structure **31** by analogy

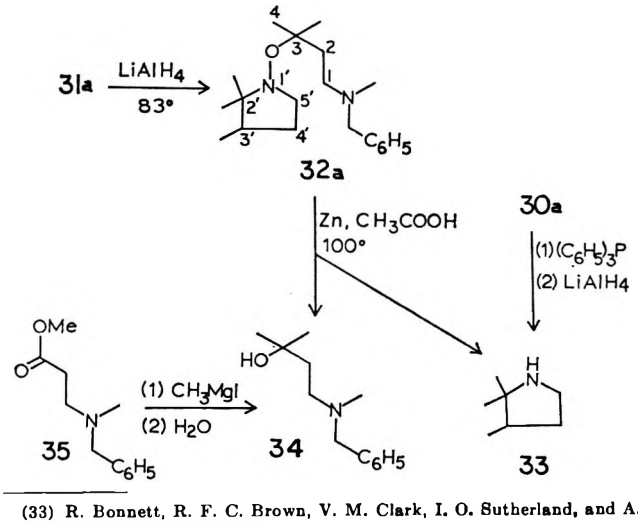


30 **31**

a, R = CH_3
b, R = H

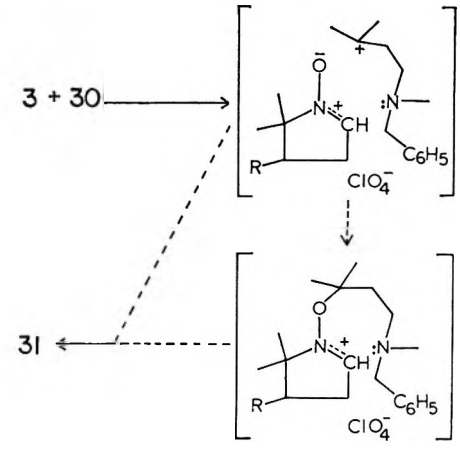
with the structures recently determined for nitrone–aziridinium salt adducts.[1] (Compound **31a** is named 6-benzyl-3,3,6,9,10,10-hexamethyl-2-oxa-1-aza-6-azoniabicyclo[5.3.0]decane perchlorate; **31b** is 6-benzyl-3,3,-6,10,10-pentamethyl-2-oxa-1-aza-6-azoniabicyclo[5.3.0]-decane perchlorate.) Formation of such a cycloadduct is representative of a new type of ring expansion, expressed generally as ④$^+$ + 3 → ⑦$^+$, in which a charged four-membered cycle combines with a 1,3-dipolar function to afford a charged seven-membered cycle. Inasmuch as infrared and nmr spectra were of no practical value in verifying structure **31**, a chemical degradative sequence was undertaken.

Upon treatment of **31a** with lithium hydride in refluxing dimethoxyethane, a free amine was obtained which showed no bands attributable to O–H or N–H in the infrared spectrum. The nmr spectrum of this material in deuteriochloroform exhibited singlets for both $ArCH_2$–N (τ 6.50) and CH_3–N (τ 7.81). The rest of the spectrum was rather complex, but upon close examination a symmetrical A_2X_2 system, which could be attributed to the C–CH_2–CH_2–N moiety, was observed at τ 7.3–7.7 and 8.1–8.5. The structure of the reduction product was thus assigned as N-methyl-N-[3-methyl-3-(2′,2′,3′-trimethylpyrrolidin-1′-oxy)butyl]-benzylamine (**32a**). This facile reduction of the C–N$^+$ bond in **31a** while the N–O bond remained intact is completely analogous to the mode of reduction of nitrone–aziridinium salt adducts.[1] Cleavage of the N–O bond in **32a** could be effected, however, by treatment with zinc dust and aqueous acetic acid at 100°. The products of this reduction were separated by glpc and were identified by comparison with authentic samples as 2,2,3-trimethylpyrrolidine (**33**) and 4-(N-benzyl-N-methylamino)-2-methyl-2-butanol (**34**). Authentic **33** was prepared as described earlier[1] by a two-step reduction of nitrone **30a**, while authentic **34** was synthesized from the amino ester **35** by treatment with excess methylmagnesium iodide. The symmetrical A_2X_2 pattern (τ 7.32 and 8.38) arising from the C–CH_2–CH_2–N grouping was displayed plainly in the nmr spectrum of **34** in deuteriochloroform. This double cleavage of adduct **31a** to form the pyrrolidine **33** and the amino alcohol **34** firmly established the assigned structure of the original adduct, that of compound **32a**, and that of **31b** as well.



One possible mechanism for the ④$^+$ + 3 → ⑦$^+$ reaction is shown in Scheme V. Opening of the azetidinium ring at the 1,2 bond to form the corresponding γ-*t*-aminocarbonium ion is postulated as the initial step. If this carbonium ion is indeed an intermediate, the experimental facts require that nitrone as solvent be more effective in assisting the fission of the 1,2 bond than either ketone or nitrile and, moreover, that nitrone addition proceed more rapidly than the elimination which supervenes in the other two cases. From this intermediate, pictured in Scheme V in correct orientation with respect to the 1,3-polarized nitrone, formation of the seven-membered heterocycle can proceed in either concerted or stepwise manner. The concerted process can be visualized as a "1,4-*polar*-1,3-*dipolar* cycloaddition." The question remains open as to whether the total process, **3** + **30** → **31**, can be concerted. On the basis of orbital symmetry considerations, the process would be allowed,[34] but the example is exceptional because of the polarity of the molecules involved, and the distinction from a nonconcerted process may vanish. The goal of building enough reactivity into a σ bond so that it behaves like a π bond continues to be an intriguing one.

SCHEME V



In summary, although there is a considerable decrease in reactivity in going from the aziridinium to the azetidinium ring system, solvolytic openings and expansions of 1,1,2,2-tetrasubstituted azetidinium salts may be effected provided that (a) the 1,2 bond is ac-

(33) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 2094 (1959).

(34) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

tivated toward polar cleavage (*e.g.*, by N-benzyl substitution) and (b) olefin formation is suppressed kinetically. The presence of α-*gem*-dimethyl substitution in the four-membered ring series led to eliminative ring opening, probably owing to the favorable stereochemistry, whereas this competing reaction did not occur in the three-membered ring series. The new reaction of a nitrone with an azetidinium salt provides an unusual seven-membered heterocyclic ring system.

Experimental Section[35]

Ethyl 3,3-Dimethylacrylate (5).—A mixture of 200 g (2.0 mol) of 3,3-dimethylacrylic acid, 500 ml of ethanol, 60 ml of concentrated sulfuric acid, and 1.3 l. of benzene was heated under reflux with stirring for 3 days in a three-necked flask fitted with two condenser–Dean-Stark trap combinations to remove the water formed during the reaction. The mixture was subsequently cooled to room temperature and washed with 3 *M* aqueous potassium carbonate. The wash layers were then extracted with additional benzene. These extracts were combined with the original organic layer, and the resulting solution was dried over anhydrous potassium carbonate and evaporated *in vacuo*. Distillation of the residue afforded 205 g (80%) of the acrylic ester as a clear colorless liquid: bp 55–61° (21 mm) (lit.[36] mp 150°); nmr (in $CDCl_3$), with satisfactory integration, at τ 4.32 (m, C=CH), 5.86 (q, CH_3CH_2—O), 7.84 and 8.11 (d, d, J = 1.0 cps, $(CH_3)_2$-C=C), and 8.75 (t, CH_3CH_2—O).

Ethyl 3-Methyl-3-methylaminobutyrate (6a).—A solution of 111.4 g (0.87 mol) of ethyl 3,3-dimethylacrylate (5) and 34.5 g (1.11 mol) of methylamine in 1 l. of ethanol was allowed to stand at room temperature for 10 days. Removal of the solvent *in vacuo* followed by distillation of the residual oil gave the amino ester as a clear colorless liquid: bp 78–83° (17 mm); yield 107.5 g (78%); ν_{max}^{film} 3340 (N–H), 1760 cm^{-1} (C=O); nmr (in $CDCl_3$), at τ 5.87 (q, CH_3CH_2—O), 7.60 (s, CH_2C=O), 7.68 (s, CH_3—N), 8.26 (s, NH), 8.74 (partially hidden triplet, CH_3CH_2—O), 8.86 (s, $(CH_3)_2C$—N).

Anal. Calcd for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.32; H, 10.64; N, 8.65.

3-Methyl-3-methylamino-1-butanol (7a).—To a stirred slurry of 19.0 g (0.5 mol) of lithium aluminum hydride in 600 ml of ether was added dropwise a solution of 47.7 g (0.3 mol) of ethyl 3-methyl-3-methylaminobutyrate (6a) in 200 ml of ether. The mixture was stirred at room temperature for 13 hr and was subsequently treated dropwise with 38 ml of water and 30 ml of 10% aqueous sodium hydroxide. The salts thus precipitated were filtered, treated with excess aqueous sodium hydroxide, and extracted with ether. The combined filtrate and extracts were dried over anhydrous potassium carbonate, filtered, and evaporated *in vacuo*. Distillation of the residual oil yielded the amino alcohol (26.5 g, 76%) as a clear colorless liquid: bp 90–91° (18 mm); ν_{max}^{film} 3300 cm^{-1} (broad, O–H and N–H); nmr (in $CDCl_3$), at τ 6.22 (t, CH_2CH_2–O), 6.44 (s, OH and NH), 7.69 (s, CH_3–N), 8.44 (t, CH_2CH_2–O), 8.88 (s, $(CH_3)_2C$–N).

Anal. Calcd for $C_6H_{15}NO$: C, 61.49; H, 12.90; N, 11.95. Found: C, 61.40; H, 12.68; N, 11.64.

N-(4-Chloro-2-methyl-2-butyl)methylamine Hydrochloride (8a).—A solution of 23.6 g (0.20 mol) of 3-methyl-3-methylamino-1-butanol (7a) in 50 ml of chloroform was added dropwise with stirring to 52.8 g (0.44 mol) of thionyl chloride cooled in an ice bath. Following the addition, the mixture was stirred at room temperature for 15 hr. At the end of this time, 30 ml of ethanol was added to destroy residual thionyl chloride. Removal of the solvent *in vacuo* afforded 32.9 g (96%) of product. An analytical sample, colorless needles from ethyl methyl ketone, had mp 137–138°; nmr (in $CDCl_3$), at τ 6.27 (t, CH_2CH_2–Cl), 7.39 (t, CH_3–N^+), 7.71 (t, CH_2CH_2–Cl), 8.52 (s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_6H_{15}Cl_2N$: C, 41.87; H, 8.79; N, 8.14. Found: C, 41.91; H, 8.75; N, 8.22.

1,2,2-Trimethylazetidine Perchlorate (9a).—Treatment of 23.6 g (0.137 mol) of N-(4-chloro-2-methyl-2-butyl)methylamine hydrochloride (8a) with 100 ml of 10% aqueous sodium hydroxide liberated the corresponding free amine, which was extracted into methylene chloride and isolated in the normal manner: yield 16.2 g (0.120 mol, 87%). This was dissolved in 400 ml of acetonitrile and added with stirring to a solution of 24.9 g (0.120 mol) of silver perchlorate in 300 ml of acetonitrile. The resulting mixture was stirred at room temperature for 27 hr. The precipitated silver chloride was then filtered and washed with additional solvent. Evaporation of the filtrate *in vacuo* yielded a solid which was treated with methylene chloride and refiltered to remove residual silver salts. Removal of the methylene chloride *in vacuo* afforded 23.8 g (quantitative from the free amino chloride) of the azetidine perchlorate. Recrystallization from ethyl acetate yielded an analytical sample as colorless needles: mp 165–166°; ν_{max}^{Nujol} 3150 cm^{-1} (N^+–H); nmr (in CF_3COOH), at τ 5.4–6.4 (m, CH_2CH_2–N^+), 7.12 (d, J = 5.5 cps, CH_3–N^+), 7.2–7.7 (m, CH_2CH_2–N^+), 8.28 and 8.31 (s,s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_6H_{14}ClNO_4$: C, 36.10; H, 7.07; N, 7.01. Found: C, 36.00; H, 6.86; N, 6.94.

1,1,2,2-Tetramethylazetidinium Perchlorate (2).—A mixture of 20.9 g (0.105 mol) of 1,2,2-trimethylazetidine perchlorate (9a) and 80 ml of 10% aqueous sodium hydroxide was extracted with methylene chloride. The combined extracts were dried over anhydrous sodium sulfiate and filtered. Approximately 200 ml of acetone was added to the filtrate, and the methylene chloride was removed by distillation at atmospheric pressure. An additional 100 ml of acetone was then added to the clear pot residue, and the resulting solution was added with stirring to a solution of 25.1 g (0.177 mol) of methyl iodide in 200 ml of acetone. The mixture was stirred for 6 hr at room temperature and was subsequently treated with 1 l. of ether to precipitate 12.4 g (52%) of the methiodide. An analytical sample, colorless cubes from ethanol, had mp 177–178° dec.

Anal. Calcd for $C_7H_{16}IN$: C, 34.86; H, 6.69. Found: C, 35.08; H, 6.74.

The methiodide (12.4 g, 51.5 mmol) was dissolved in 600 ml of methanol and added to a solution of 10.7 g (51.5 mmol) of silver perchlorate in 400 ml of methanol. The mixture was stirred at room temperature for 5 hr, after which time the precipitated silver iodide was filtered and washed with solvent. Removal of the methanol *in vacuo* afforded 10.6 g (89% from the methiodide) of the azetidinium perchlorate. The analytical sample, colorless cubes from ethanol, had mp 172.5–173.0°; nmr (in CF_3COOH), at τ 5.83 (t, CH_2CH_2–N^+), 6.90 (s, $(CH_3)_2N^+$), 7.35 (broadened triplet, CH_2CH_2–N^+), 8.25 (s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_7H_{16}ClNO_4$: C, 39.35; H, 7.55; N, 6.56. Found: C, 39.24; H, 7.36; N, 6.29.

Ethyl 3-Benzylamino-3-methylbutyrate (6b).—A solution of 128 g (1.0 mol) of ethyl 3,3-dimethylacrylate (5) and 118 g (1.1 mol) of benzylamine in 1 l. of ethanol was heated at 50–55° for 15 days. Subsequent removal of the solvent *in vacuo* followed by fractional distillation of the residual oil afforded 121 g (52%) of the product as a clear colorless liquid: bp 115–117° (0.55 mm); ν_{max}^{film} 3350 (N–H), 1740 cm^{-1} (C=O); nmr (in $CDCl_3$), at τ 2.69 (s, C_6H_5), 5.87 (q, CH_3CH_2–O), 6.28 (s, $ArCH_2$–N), 7.51 (s, CH_2C=O), 7.87 (s, NH), 8.77 (singlet over triplet, $(CH_3)_2C$–N and CH_3CH_2–O).

Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.96. Found: C, 71.63; H, 9.01; N, 6.09.

3-Benzylamino-3-methyl-1-butanol (7b).—A solution of 141 g (0.6 mol) of ethyl 3-benzylamino-3-methylbutyrate (6b) in 300 ml of ether was added dropwise to a stirred slurry of 37.9 g (1.0 mol) of lithium aluminum hydride in 1 l. of ether. The mixture was stirred for 18 hr at room temperature and was then treated dropwise with 76 ml of water and 61 ml of 10% aqueous sodium hydroxide. The precipitated salts were filtered and washed with ether. The filtrate was then dried over anhydrous potassium carbonate and was subsequently evaporated *in vacuo*. Distillation of the residue yielded 97.5 g (84%) of the amino alcohol as a clear colorless liquid: bp 119–121° (0.45 mm); ν_{max}^{film} 3300 cm^{-1} (broad, O–H and N–H); nmr (in $CDCl_3$), at τ 2.72 (s, C_6H_5), 6.18 (partially hidden triplet, CH_2CH_2–O), 6.29 (s,

(35) All melting points are corrected; boiling points are uncorrected. Infrared spectra were obtained with Perkin-Elmer grating spectrophotometers, Models 521 or 337. Nmr spectra were obtained on a Varian Associates Model A-60 or A-60A spectrometer using tetramethylsilane as either an external or internal standard. Glpc analyses were carried out on an F & M Model 300 gas chromatograph using a 0.25-in. column of 20% Carbowax 20 M (1 m) on either Anakrom ABS or Chromosorb W, HMDS treated. We are indebted to Mr. J. Nemeth and his associates for the microanalyses and molecular weight determinations.

(36) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

$ArCH_2$–N), 6.53 (s, OH), 8.39 (t, CH_2CH_2–O), 8.80 (s, $(CH_3)_2$-C–N).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.56; H, 9.91; N, 7.25. Found: C, 74.44; H, 9.80; N, 7.05.

N-(4-Chloro-2-methyl-2-butyl)benzylamine Hydrochloride (8b).—A solution of 97.5 g (0.5 mol) of 3-benzylamino-3-methyl-1-butanol (**7b**) in 125 ml of chloroform was added dropwise with stirring to 131 g (1.1 mol) of thionyl chloride cooled in an ice bath. Following the addition, the ice bath was removed and the reaction mixture was stirred at room temperature for 12 hr, during which time the product solidified. The residual thionyl chloride was decomposed by treatment with 75 ml of ethanol. Addition of excess ether to the resulting solution reprecipitated the product, which was filtered and washed with ether to yield 124.4 g (quantitative). Recrystallization from ethyl acetate afforded an analytical sample as colorless needles: mp 170–172°; nmr (in D_2O), at τ 2.03 (s, C_6H_5), 4.86 (s, $ArCH_2$–N^+), 5.78 (t, CH_2CH_2–Cl), 7.23 (t, CH_2CH_2–Cl), 8.04 (s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_{12}H_{19}Cl_2N$: C, 58.06; H, 7.71; N, 5.65. Found: C, 58.31; H, 7.77; N, 5.79.

1-Benzyl-2,2-dimethylazetidine Perchlorate (9b).—Treatment of 49.6 g (0.2 mol) of N-(4-chloro-2-methyl-2-butyl)benzylamine hydrochloride (**8b**) with 700 ml of 3% aqueous sodium hydroxide liberated the free amino chloride which was extracted into methylene chloride. Following the normal isolation procedure, this amine was dissolved in 400 ml of acetone and added with stirring to a solution of 41.5 g (0.2 mol) of silver perchlorate in 500 ml of acetone. Silver chloride began to precipitate almost immediately. After being stirred at room temperature for 40 hr, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residual oil was treated with methylene chloride and filtered in order to remove any residual silver salts. Removal of the methylene chloride *in vacuo* afforded the desired azetidine salt, which was recrystallized from isopropyl alcohol as colorless plates: mp 151.0–151.5°; yield 46.8 g (85%); ν_{max}^{Nujol} 3120 cm^{-1} (N^+–H); nmr (in CF_3COOH), at τ 2.52 (s, C_6H_5), 5.6–6.1 (m, $ArCH_2$–N^+ and CH_2CH_2–N^+), 7.1–7.9 (m, CH_2CH_2–N^+), 8.17 and 8.35 (s, s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_{12}H_{18}ClNO_4$: C, 52.27; H, 6.58; N, 5.08. Found: C, 52.30; H, 6.59; N, 4.84.

1-Benzyl-1,2,2-trimethylazetidinium Perchlorate (3) and Bromide.—Upon treatment with 600 ml of 3% aqueous sodium hydroxide, 46.8 g (0.17 mol) of 1-benzyl-2,2-dimethylazetidine perchlorate (**9b**) was converted into the corresponding free azetidine. This was isolated in the usual manner, and was subsequently dissolved in 400 ml of acetone and added dropwise with stirring to a solution of 35.5 g (0.25 mol) of methyl iodide in 400 ml of acetone. Upon heating the resulting solution in a water bath maintained at approximately 50°, the methiodide precipitated. After 4 hr of heating and stirring, the mixture was treated with excess ether and filtered to yield 50.5 g (94%) of the methiodide, mp 137–138° dec.

To a stirred solution of 50.5 g (0.16 mol) of the azetidinium iodide in 1.6 l. of methanol was added a solution of 33.2 g (0.16 mol) of silver perchlorate in 400 ml of methanol. After being stirred at room temperature for 1 hr, the mixture was filtered and the filtrate was evaporated *in vacuo*, yielding the azetidinium perchlorate in a crystalline form. A second crop of crystals was obtained by treatment of the precipitated silver iodide with hot methanol followed by filtration and removal of the solvent *in vacuo*. The total yield of product was 42.8 g (93% from the methiodide). One recrystallization from methanol afforded an analytical sample as colorless prisms: mp 142.5–143.0°; nmr (in CF_3COOH), at τ 2.45 (s, C_6H_5), 5.36 and 5.80 (AB system, J = 13.0 cps, $ArCH_2$–N^+), 5.1–5.7 and 6.1–6.6 (m, m, CH_2CH_2–N^+), 7.07 (s, CH_3–N^+), 6.9–7.5 (m, CH_2CH_2–N^+), 8.00 and 8.25 (s, s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_{13}H_{20}ClNO_4$: C, 53.88; H, 6.96; N, 4.83. Found: C, 53.86; H, 6.92; N, 4.84.

For the conversion of perchlorate into **1-benzyl-1,2,2-trimethylazetidinium bromide**, a column of 14.5 g (wet weight, 20 mequiv) of Dowex 1-X8 chloride (200–400 mesh) was washed thoroughly with water and treated with 300 ml of 10% aqueous potassium bromide. Water was then passed through the column until the eluent gave no precipitate with silver nitrate. A solution of 580 mg (2.0 mmol) of 1-benzyl-1,2,2-trimethylazetidinium perchlorate (**3**) in 175 ml of water was then passed through the column, followed by water until the eluent gave no precipitate with silver nitrate. The collected eluent was evaporated *in vacuo* and the residue was treated with ether and filtered to yield 540 mg (quantitative) of the azetidinium bromide. An analytical sample, colorless prisms from isopropyl alcohol, had mp 141–144° dec.

Anal. Calcd for $C_{13}H_{20}BrN$: C, 57.78; H, 7.46; N, 5.19. Found: C, 57.81; H, 7.40; N, 5.22.

The crystals thus obtained were judged to be suitable for X-ray analysis, and Professor L. Trefonas of Louisiana State University, New Orleans, has the compound presently under crystallographic study.

Determination of the Molecular Weight of Azetidinium Salt 3.—Apparent molecular weights of the azetidinium perchlorate and benzyltrimethylammonium perchlorate (**11**) were determined at various concentrations in acetone using a Mecrolab vapor pressure osmometer. The data obtained are recorded in Table I and are plotted in Figure 1.

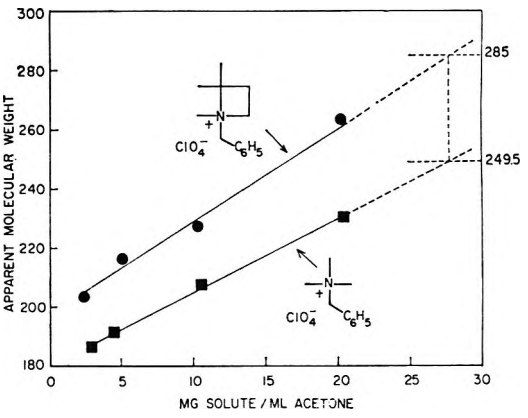


Figure 1.—The apparent molecular weights of **3** and **11** *vs.* concentration in acetone.

TABLE I

APPARENT MOLECULAR WEIGHTS OF **3** AND **11** IN ACETONE

Compd	Concn, mg/ml of acetone	Apparent mol wt
3	2.178	204
	4.990	217
	10.13	228
	20.10	264
	(27.8)	(285)
11	2.745	187
	4.336	192
	10.45	208
	20.26	231
	(27.8)	(249.5)

By extrapolation of the roughly parallel plots to the concentration at which the apparent molecular weight of **11** is equivalent to its theoretical molecular weight (249.5), a comparable value of 285 is obtained for the molecular weight of **3** (theoretical 289.5).

Benzyltrimethylammonium Perchlorate (11).—To a stirred solution of 13.5 g (0.10 mol) of benzyldimethylamine in 20 ml of ethanol was added dropwise 19.0 g (0.13 mol) of methyl iodide. Following the addition, the mixture was heated under reflux for 45 min and was then cooled to room temperature. Upon the addition of 100 ml of ether, the methiodide precipitated and was filtered, yield 27.1 g (98%).

A solution of 8.3 g (0.03 mol) of the benzyltrimethylammonium iodide in 100 ml of methanol was added with stirring to a solution of 6.2 g (0.03 mol) of silver perchlorate in 50 ml of methanol. The mixture was stirred at room temperature for several hours and then filtered. Upon removal of the solvent *in vacuo*, 7.0 g (94% from the methiodide) of the perchlorate salt was obtained. Recrystallization from ethanol yielded an analytical sample as colorless plates: mp 129.5–131.0° (lit.[37] mp 126–127°); nmr (in CH_2Cl_2), at τ 2.50 (s, C_6H_5), 5.46 (s, $ArCH_2$–N^+), 6.89 (s, $(CH_3)_3N^+$).

Anal. Calcd for $C_{10}H_{16}ClNO_4$: C, 48.10; H, 6.46; N, 5.61. Found: C, 47.99; H, 6.37; N, 5.32.

(37) F. Schlegel, *Ber.*, **64**, 1739 (1931).

Attempted Benzylation of 1-Benzyl-2,2-dimethylazetidine (12).—A mixture of 2.76 g (10.0 mmol) of 1-benzyl-2,2-dimethylazetidine perchlorate (**9b**) and 30 ml of 3% aqueous sodium hydroxide was extracted with methylene chloride and worked up as usual to yield 1.70 g (97%) of free **1-benzyl-2,2-dimethylazetidine (12)** as a colorless liquid. This was cooled in an ice bath and treated dropwise with 3.42 g (20.0 mmol) of benzyl bromide. The ice bath was removed following the addition and the mixture was stirred at room temperature for 20 hr. Subsequent treatment with excess ether precipitated **1-benzyl-2,2-dimethylazetidine hydrobromide (13)** as a white solid which was filtered and washed with ether to yield 1.04 g (42% from the free azetidine): mp 147–149°; nmr (in D_2O), at τ 2.47 (s, C_6H_5), 5.72 (s, $ArCH_2$–N^+), 5.9–6.3 (unresolved multiplet, CH_2CH_2–N^+), 7.60 (t, CH_2CH_2–N^+), 8.32 (s, $(CH_3)_2C$–N^+).

The ethereal filtrate obtained from the above work-up procedure was concentrated *in vacuo* and extracted with 3% aqueous hydrochloric acid. These extracts were then made basic by the addition of excess 10% aqueous sodium hydroxide and the resulting mixture was extracted with methylene chloride. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* to yield a clear colorless liquid that was primarily **N-(3-methyl-3-buten-1-yl)dibenzylamine (14)**; nmr (in $CDCl_3$) absorptions appeared at τ 2.72 (m, C_6H_5), 5.35 (apparent singlet, C=CH_2), 6.45 (s, $(ArCH_2)_2N$), 7.3–8.0 (A_2B_2 system, C—CH_2CH_2—N), 8.43 (s, CH_3—C=C). A small amount of unreacted 1-benzyl-2,2-dimethylazetidine was also present, as evidenced by a singlet at τ 8.80 for $(CH_3)_2C$–N.

Ethyl 3-Dibenzylamino-3-methylbutyrate (15).—To a stirred mixture of 23.5 g (0.10 mol) of ethyl 3-benzylamino-3-methylbutyrate (**6b**) and 20.7 g (0.15 mol) of anhydrous potassium carbonate in 150 ml of ethanol was added 18.8 g (0.11 mol) of benzyl bromide. After being heated under gentle reflux with stirring for 24 hr, the mixture was brought to alkalinity with potassium hydroxide pellets and filtered. The filtrate was evaporated *in vacuo*, and the residue was combined with the previously filtered inorganic salts and treated with 10% aqueous sodium hydroxide. The resulting mixture was extracted with ether, and the combined extracts were dried over anhydrous potassium carbonate and evaporated *in vacuo*. Preliminary distillation of the residual oil through a short Vigreux column yielded 3.5 g of starting material, bp 95–100° (0.10 mm). The resulting pot residue was then distilled through a short-path head to afford the dibenzylamino ester as a clear colorless oil: bp 160–162° (0.03 mm); yield 20.6 g (63%); no N–H band in the infrared spectrum; nmr (in $CDCl_3$), at τ 2.6–3.0 (m, C_6H_5), 5.86 (q, CH_3CH_2–O), 6.25 (s, $(ArCH_2)_2N$), 7.43 (s, CH_2C=O), 8.78 (singlet over triplet, $(CH_3)_2C$–N and CH_3CH_2–O).

Anal. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.31. Found: C, 77.43; H, 8.38; N, 4.31.

3-Dibenzylamino-3-methyl-1-butanol (16).—A solution of 19.8 g (0.061 mol) of ethyl 3-dibenzylamino-3-methylbutyrate (**15**) in 50 ml of ether was added dropwise with stirring to a slurry of 5.3 g (0.14 mol) of lithium aluminum hydride in 150 ml of ether. The resulting mixture was stirred for 6 hr at room temperature. Work-up was then effected by the dropwise addition of 100 ml of water and 50 ml of 10% aqueous sodium hydroxide. The ethereal solution was decanted from the resulting gel which was subsequently extracted with additional ether. The combined ethereal layers were dried over anhydrous potassium carbonate, filtered, and evaporated *in vacuo* to yield the crystalline product. Recrystallization from hexane afforded an analytical sample as colorless prisms: mp 86–87°; yield 14.6 g (85%); $\nu_{max}^{CHCl_3}$ 3240 cm^{-1} (broad, O–H); nmr (in $CDCl_3$), at τ 2.82 (s, C_6H_5), 5.10 (s, OH), 6.14 (partially hidden triplet, CH_2CH_2–O), 6.23 (s, $(ArCH_2)_2N$), 8.18 (t, CH_2CH_2–O), 8.88 (s, $(CH_3)_2C$–N).

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94. Found: C, 80.43; H, 8.88; N, 4.89.

N-(4-Chloro-2-methyl-2-butyl)dibenzylamine Hydrochloride (17).—A solution of 14.2 g (0.05 mol) of 3-dibenzylamino-3-methyl-1-butanol (**16**) in 35 ml of chloroform was added dropwise with stirring to 11.9 g (0.10 mol) of thionyl chloride cooled in an ice bath. The ice bath was removed following the addition, and the reaction was allowed to proceed at room temperature for 6 hr. At the end of this time, 5 ml of ethanol was added to decompose any residual thionyl chloride. Evaporation of the resulting mixture *in vacuo* yielded an oil which was taken up in ethanol and treated with excess ether to precipitate 16.6 g (98%) of the desired salt. Recrystallization from ethyl methyl ketone afforded an analytical sample as a white amorphous powder: mp 156–157°; nmr (in $CDCl_3$), at 2.4–3.0 (m, C_6H_5), 5.3–6.2 (m, $(ArCH_2)_2N^+$), 6.32 (s, CH_2CH_2–Cl), 7.31 (t, CH_2CH_2–Cl), 8.23 (s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_{19}H_{25}Cl_2N$: C, 67.45; H, 7.45; N, 4.14. Found: C, 67.43; H, 7.54; N, 3.85.

Attempted Cyclization of N-(4-Chloro-2-methyl-2-butyl)dibenzylamine (18).—A mixture of 2.70 g (8.0 mmol) of N-(4-chloro-2-methyl-2-butyl)dibenzylamine hydrochloride (**17**) and 15 ml of 3% aqueous sodium hydroxide was extracted with methylene chloride. Following the normal work-up procedure, there was obtained 2.39 g (99%) of free **N-(4-chloro-2-methyl-2-butyl)dibenzylamine (18)** as colorless crystals; nmr (in $CDCl_3$) signals appeared at τ 2.79 (s, C_6H_5), 6.30 (singlet over triplet, $(ArCH_2)_2N$ and CH_2CH_2–Cl), 7.96 (t, CH_2CH_2–Cl), 8.95 (s, $(CH_3)_2C$–N).

This amino chloride was dissolved in 30 ml of acetone and added to a stirred solution of 1.65 g (7.9 mmol) of silver perchlorate in 30 ml of acetone. The resulting mixture was stirred at room temperature for 44 hr, during which time silver chloride precipitated slowly and continuously. The silver chloride was subsequently removed by filtration and the filtrate was evaporated *in vacuo* to yield a turbid oil. This was treated with methylene chloride and refiltered to remove residual silver salts. Removal of the methylene chloride *in vacuo* yielded an oil which was dissolved in hot ethyl acetate and treated with ether to precipitate 0.50 g (17%) of **N-(4-chloro-2-methyl-2-butyl)dibenzylamine perchlorate (19)**. An analytical sample, colorless prisms from ethyl acetate, had mp 161.5–162.0°; ν_{max}^{Nujol} 3080 cm^{-1} (shoulder, N^+–H); nmr (in CF_3COOH), at τ 2.5–3.0 (m, C_6H_5), 5.16 and 5.64 (AB system split into doublets, J_{AB} = 13.6 cps, J_{vic} = 3.3 cps, $J_{vic'}$ = 6.5 cps, $(ArCH_2)_2N^+H$), 6.12 (t, CH_2CH_2–Cl), 7.39 (t, CH_2CH_2–Cl), 8.25 (s, $(CH_3)_2C$–N^+).

Anal. Calcd for $C_{19}H_{25}Cl_2NO_4$: C, 56.72; H, 6.26; N, 3.48; Cl, 17.63. Found: C, 56.86; H, 6.30; N, 3.25; Cl, 17.73.

Reaction of 1-Benzyl-2,2-dimethylazetidine Perchlorate (9b) with Diazomethane.—An ethereal solution of diazomethane was added in small aliquots to a stirred solution of 1.00 g (3.63 mmol) of the azetidine perchlorate in 40 ml of acetonitrile maintained at 0–5°. As the diazomethane solution was added, decolorization occurred, and bubbles of nitrogen were evolved from the reaction mixture. When the yellow color finally persisted, the addition was terminated and the resulting solution was stirred at 0° for 30 min. A small amount of glacial acetic acid was then added to remove excess diazomethane, and the acetonitrile was removed *in vacuo*. Treatment of the residue with ethyl acetate afforded 534 mg (51%) of **1-benzyl-1,2,2-trimethylazetidinium perchlorate (3)**, mp 140–141°, identified by its infrared spectrum (Nujol).

Attempted Reaction of Azetidine Salt 9b with Phenyldiazomethane.—A solution of 1.13 g (9.6 mmol) of phenyldiazomethane, prepared according to the precedure of Farnum,[38] in 30 ml of acetonitrile was added dropwise with stirring to a solution of 2.48 g (9.0 mmol) of the azetidine perchlorate in 70 ml of acetonitrile. There was no visible evolution of nitrogen during the addition. The reaction mixture was stirred at room temperature for 5 hr and was then treated with a small amount of glacial acetic acid to decompose unreacted phenyldiazomethane. The acetonitrile was removed *in vacuo;* then the residue was treated with ethyl acetate to yield 1.81 g (73% recovery) of starting material, mp 150–151°.

N-(3-Chloropropyl)piperidine Hydrochloride (20).—A solution of 10.0 g (0.07 mol) of N-(3-hydroxypropyl)piperidine (available from the Aldrich Chemical Co., Inc.) in 20 ml of chloroform was added dropwise with stirring to 16.7 g (0.14 mol) of thionyl chloride cooled in an ice bath. Following the addition, the mixture was warmed to room temperature and was stirred for 15 hr. The product was subsequently precipitated by the addition of 100 ml of ether. Recrystallization from ethyl acetate–isopropyl alcohol afforded an analytical sample as colorless needles: mp 225–226° (lit.[31] mp 215–216°); yield 11.4 g (83%); nmr (in D_2O), at τ 5.6–6.8 (complex multiplets, CH_2–N^+–CH_2, CH_2–N^+, and CH_2–Cl), 7.0–8.2 (complex multiplets, C–CH_2–C and C–$(CH_2)_3$–C).

Anal. Calcd for $C_8H_{17}Cl_2N$: C, 48.50; H, 8.64; N, 7.07. Found: C, 48.30; H, 8.60; N, 6.91.

4-Azoniaspiro[3.5]nonane Perchlorate (21). A. From N-(3-Chloropropyl)piperidine and Silver Perchlorate.—Treatment of 8.0 g (0.04 mol) of N-(3-chloropropyl)piperidine hydrochloride

(38) D. G. Farnum, *J. Org. Chem.*, **28**, 870 (1963).

(20) with 100 ml of 4% aqueous sodium hydroxide liberated the free chloropropylpiperidine, which was extracted into methylene chloride and isolated in the usual manner. This was dissolved in 100 ml of acetone and added to a stirred solution of 8.3 g (0.04 mol) of silver perchlorate in 100 ml of acetone. Silver chloride slowly precipitated as a fine black powder. The mixture was stirred for 48 hr with intermittent heating in a warm water bath (50–60°). Subsequent filtration of the silver chloride and evaporation of the filtrate solvent *in vacuo* yielded an oily residue which solidified upon treatment with isopropyl alcohol. Recrystallization from isopropyl alcohol afforded the product as colorless needles: mp 172–173°; yield 4.3 g (48%); nmr (in D_2O), at τ 5.32 (t, azetidinium CH_2–N^+), 6.10 (m, piperidinium CH_2–N^+), 6.6–7.2 (m, C–CH_2–C), 7.5–8.1 (unresolved multiplet, C–$(CH_2)_3$–C).

Anal. Calcd for $C_8H_{16}ClNO_4$: C, 42.57; H, 7.15; N, 6.21. Found: C, 42.75; H, 7.21; N, 5.99.

B. **From N-(3-Chloropropyl)piperidine at 100°.**—A mixture of 2.39 g (14.8 mmol) of N-(3-chloropropyl)piperidine (liberated from 3.03 g of the hydrochloride salt 20 as described above) and 25 ml of water was heated at 100° for 5 hr. Subsequent removal of the water *in vacuo* afforded 2.65 g of **4-azoniaspiro[3.5]nonane chloride** (22, X = Cl) as a syrup, presumably in a hydrated form. A picrate prepared from this material crystallized from 95% ethanol as yellow needles, mp 239–240° (lit.[26] mp 239–240°).

A solution of 1.07 g of the hydrated chloride 22 in 20 ml of methanol was treated with 1.24 g (6.0 mmol) of silver perchlorate in 10 ml of methanol, precipitating silver chloride immediately. The resulting mixture was stirred for 1 hr and was then filtered. Evaporation of the filtrate *in vacuo* afforded a dark solid, which was treated with methylene chloride and refiltered to remove residual silver salts. Removal of the methylene chloride *in vacuo* yielded the desired quaternary perchlorate, which was recrystallized from isopropyl alcohol as colorless needles (1.05 g), mp 170–171°. Infrared and nmr spectra of this salt were identical with those of the product obtained by procedure A.

Attempted Methanolysis of 1,1,2,2-Tetramethylazetidinium Perchlorate (2).—A solution of 500 mg (2.34 mmol) of the azetidinium salt in 25 ml of methanol was heated under reflux for 35 hr. The solvent was then removed *in vacuo* to yield 498 mg of solid material. Recrystallization from methanol–ether afforded 253 mg (51% recovery) of starting material, mp 173–174°. The mother liquor from the recrystallization was evaporated *in vacuo* to yield 174 mg of an impure solid, mp 114–140°. The nmr spectrum of this material (in CF_3COOH) indicated that it was primarily starting material; no methanolysis product could be detected.

Reaction of Azetidinium Salt 2 with Sodium Methoxide.—A mixture of 500 mg (2.34 mmol) of the azetidinium salt and 1.10 g (20.4 mmol) of sodium methoxide in 30 ml of methanol was stirred at room temperature for 3 days. The mixture was then acidified with ethereal hydrogen chloride and evaporated *in vacuo*. Treatment of the residue with excess 6% aqueous sodium hydroxide liberated an amine which was extracted into ether. The extracts were dried over anhydrous potassium carbonate and filtered, and most of the ether was removed by slow distillation through a 6-in. Vigreux column. The residual liquid was determined (by nmr analysis) to be a mixture of ether and 176 mg (67%) of **N-(3-methyl-3-buten-1-yl)dimethylamine (24)**; nmr (in $CDCl_3$) signals appeared at τ 5.28 (apparent singlet, C=CH_2), 7.6–7.8 (partially hidden multiplet, C–CH_2CH_2–N), 7.78 (s, $(CH_3)_2N$), 8.26 (s, CH_3–C=C).

Attempted Reaction of Azetidinium Salt 2 with Acetone.—A solution of 500 mg (2.34 mmol) of the azetidinium perchlorate in 40 ml of acetone was heated under reflux for 5 days. The acetone was subsequently removed *in vacuo*. Treatment of the residue with ether afforded 495 mg (99%) of starting material, mp 172–173°.

Attempted Hydrogenolysis of Azetidinium Salt 2.—A suspension of 500 mg (2.34 mmol) of the azetidinium salt in 75 ml of ethanol was shaken under 3 atm of hydrogen for 25 hr in the presence of 250 mg of Adams catalyst. The mixture was then filtered and the catalyst was washed with acetonitrile to dissolve the crystalline material present. Removal of the solvents *in vacuo* afforded 472 mg (94% recovery) of starting material, mp 173–175°.

Methanolysis of 1-Benzyl-1,2,2-trimethylazetidinium Perchlorate (3).—A solution of 1.00 g (3.46 mmol) of the azetidinium perchlorate in 25 ml of methanol was heated under reflux for 16 hr. Removal of the solvent *in vacuo* and trituration of the residue with ether afforded 1.05 g of crude product. Two recrystallizations from ethyl acetate–ether yielded an analytical sample of **N-(3-methoxy-3-methylbutyl)-N-methylbenzylamine perchlorate (25a)** as colorless needles: mp 113.0–113.5°; ν_{max}^{Nujol} 3070 cm^{-1} (shoulder, N^+–H); nmr (in CF_3COOH), at τ 2.42 (s, C_6H_5), 5.60 (d, J = 5.5 cps, $ArCH_2$–N^+), 6.2–6.7 (unresolved multiplet, CH_2CH_2–N^+), 6.65 (s, CH_3–O), 6.96 (d, J = 5.0 cps, CH_3–N^+), 7.90 (t, CH_2CH_2–N^+), 8.65 and 8.85 (s, s, $(CH_3)_2$C–O).

Anal. Calcd for $C_{14}H_{24}ClNO_5$: C, 52.25; H, 7.52; N, 4.35. Found: C, 52.54; H, 7.70; N, 4.19.

Treatment of the crude methanolysis product with 3% aqueous sodium hydroxide liberated an amine mixture which was extracted into methylene chloride and isolated as usual. Glpc analysis (200°) and nmr spectra of the mixture indicated the presence of two components, **N-(3-methoxy-3-methylbutyl)-N-methylbenzylamine (27a)** (68%) and **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine (29)** (32%). The amino ether exhibited nmr (in $CDCl_3$) signals at τ 2.76 (s, C_6H_5), 6.58 (s, $ArCH_2$–N), 6.93 (s, CH_3–O), 7.4–7.8 (partially hidden multiplet, CH_2CH_2–N), 7.88 (s, CH_3–N), 8.40 (partially hidden triplet, CH_2CH_2–N), 8.92 (s, $(CH_3)_2$C–O); no signal ascribable to CH_2–O was detected.

Nmr Study of the Methanolysis of Azetidinium Salt 3.—A suspension of 2.00 g (6.92 mmol) of the azetidinium perchlorate in 50 ml of methanol was prepared (t = 0) and heated rapidly to reflux temperature. Aliquots (3.0 ml) were removed from the reaction mixture every 30 min for the first 3 hr, and every 60 min thereafter. Each aliquot was immediately placed in a test tube chilled in an ice bath so as to precipitate any azetidinium salt present and thus effectively quench the reaction. Following refrigeration for a short period, the methanol was removed from each aliquot *in vacuo* at room temperature. Nmr spectra (in CF_3COOH) of the resulting solids were then obtained to determine the composition of the mixtures. The spectrum of each fraction was run as soon as possible after the addition of trifluoroacetic acid because of the lability of the reaction products, N-(3-methoxy-3-methylbutyl)-N-methylbenzylamine perchlorate (25a) and N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine perchlorate (28), in that solvent. The composition of each fraction was determined as follows: (a) the singlet at τ 6.65 (CH_3–O in 25a) provided a direct measure of 25a; (b) the combined signals at τ 7.8–8.0 (CH_2CH_2–N^+ in 25a and three protons of $(CH_3)_2$C–N^+ in 3 provided a measure of 25a + 3 and therefore, by difference, a measure of 3; (c) the singlet at τ 2.4–2.5 (C_6H_5 in 3, 25a, and 28) provided a measure of all three components combined and thus, by difference, a measure of 28. The calculated molar percentage compositions of each fraction are given in Table II,

Table II

Composition of the Reaction Mixture during the Methanolysis of Azetidinium Salt 3

Time, hr	[3], mole %	[25a], mole %	[28], mole %
0.5	92	8	0
1.0	76	21	3
1.5	62	30	8
2.0	51	38	11
2.5	41	45	14
3.0	31	52	17
4.0	21	57	22
5.0	12	64	24
6.0	15	65	20
7.0	5	68	27
8.0	2	69	29
9.0	4	73	23
10.0	2	72	26
11.0	1	74	25
12.0	0	74	26
13.0	0	76	24

and these data are plotted as a function of time in Figure 2. Certain deficiencies in the analytical procedure may be noted. Thus, zero time corresponded to the mixing of reactants at room temperature, and a finite amount of time was required to bring the system to reflux. The apparent continuing increase in the concentration of 25a after 8 hr is probably not real since there is

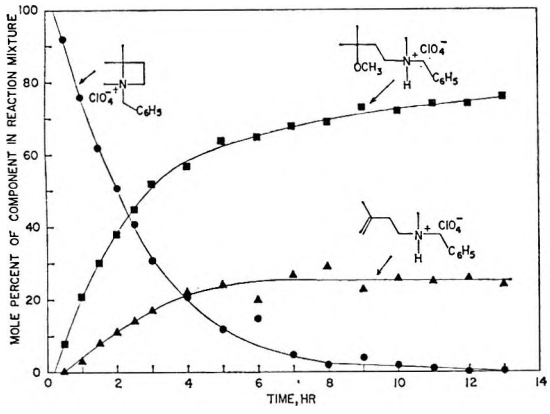


Figure 2.—Methanolysis of 1-benzyl-1,2,2-trimethylazetidinium perchlorate at reflux (~65°).

no accompanying increase or decrease in the concentration of **28** after that time. Nevertheless, it was readily determined from these data that the reaction is essentially complete after 8 hr, and that the methanolysis proceeds at a rate approximately three times that of the thermal elimination.

Ethanolysis of Azetidinium Salt 3.—A suspension of 1.00 g (3.46 mmol) of the azetidinium perchlorate in 50 ml of ethanol was heated under reflux with stirring for 28 hr. Subsequent removal of the solvent *in vacuo* yielded an oil which was taken up into ethyl acetate. Addition of ether precipitated 0.51 g of crude product. Recrystallization from ethyl acetate–ether afforded an analytical sample of **N-(3-ethoxy-3-methylbutyl)-N-methylbenzylamine perchlorate (25b)** as colorless prisms: mp 74–75°; $\nu_{max}^{CHCl_3}$ 3070 cm^{-1} (shoulder, N$^+$–H); nmr (in $CDCl_3$), at τ 2.52 (s, C_6H_5), 5.57 (d, J = 5.0 cps, $ArCH_2$–N$^+$), 6.4–6.9 (hidden multiplet, CH_2CH_2–N$^+$), 6.61 (q, CH_3CH_2–O), 7.01 (d, J = 4.5 cps, CH_3–N$^+$), 8.10 (unresolved triplet, CH_2CH_2–N$^+$), 8.80 and 8.96 (s, s, $(CH_3)_2C$–O), 8.88 (partially hidden triplet, CH_3CH_2–O).

Anal. Calcd for $C_{15}H_{26}ClNO_5$: C, 53.65; H, 7.80; N, 4.17. Found: C, 53.75; H, 7.86; N, 4.08.

The crude ethanolysis product was treated with 5% aqueous sodium hydroxide, and the amine mixture thus liberated was extracted into ether and worked up as usual. Glpc analysis (200°) and nmr spectra of this mixture demonstrated the presence of two components, **N-(3-ethoxy-3-methylbutyl)-N-methylbenzylamine (27b)** (58%) and **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine (29)** (42%). The amino ether exhibited nmr (in $CDCl_3$) signals at τ 2.71 (s, C_6H_5), 6.51 (s, $ArCH_2$–N), 6.67 (partially hidden quartet, CH_3CH_2–O), 7.3–7.7 (partially hidden multiplet, CH_2CH_2–N), 7.81 (s, CH_3–N), 8.2–8.5 (partially hidden triplet, CH_2CH_2–N), 8.86 (s, $(CH_3)_2C$–O), 8.91 (t, CH_3CH_2–O).

Reaction of Azetidinium Salt 3 with Sodium Methoxide.—A mixture of 1.00 g (3.46 mmol) of the azetidinium perchlorate and 1.60 g (29.6 mmol) of sodium methoxide in 30 ml of acetonitrile was stirred at room temperature for 18 hr. At the end of this time, the mixture was treated with aqueous sodium hydroxide and extracted with ether. Drying of the extracts over anhydrous potassium carbonate and evaporation of the solvent *in vacuo* afforded **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine (29)** as a yellow oil; nmr (in CCl_4) signals appeared at τ 2.82 (s, C_6H_5), 5.34 (apparent singlet, C=CH_2), 6.59 (s, $ArCH_2$–N), 7.4–8.0 (partially hidden multiplet, C–CH_2–CH_2–N), 7.89 (s, CH_3–N), 8.32 (s, CH_3–C=C).

Reaction of Azetidinium Salt 3 with Acetone.—A solution of 2.00 g (6.91 mmol) of the azetidinium salt in 50 ml of acetone was heated under reflux for 6 days. Subsequent removal of the solvent *in vacuo* afforded an oil which eventually crystallized after repeated treatments with ether. Chromatography on silica gel using ethyl acetate for elution yielded 0.79 g (40%) of **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine perchlorate (28)**. An analytical sample, colorless plates from ethyl acetate–ether, had mp 107–109°; $\nu_{max}^{CHCl_3}$ 3070 (shoulder, N$^+$–H), 1650, 905 cm^{-1} (C=CH_2); nmr (in $CDCl_3$), at τ 2.55 (s, C_6H_5), 5.20 (apparent singlet, C=CH_2), 5.61 (d, J = 5.5 cps, $ArCH_2$–N$^+$), 6.4–6.9 (m, C–CH_2CH_2–N$^+$), 7.07 (d, J = 4.5 cps, CH_3–N$^+$), 7.51 (t, C–CH_2–CH_2–N$^+$), 8.32 (s, CH_3–C=C).

Anal. Calcd for $C_{13}H_{20}ClNO_4$: C, 53.88; H, 6.96; N, 4.83. Found: C, 54.12; H, 7.15; N, 4.59.

Reaction of Azetidinium Salt 3 with Acetonitrile.—A solution of 500 mg (1.73 mmol) of the azetidinium perchlorate in 50 ml of acetonitrile was heated under reflux for 3 days. The acetonitrile was then removed *in vacuo*, and the residue was treated with ether and filtered to yield 483 mg (97%) of **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine perchlorate (28)**.

Reaction of Azetidinium Salt 3 with Sodium Iodide.—A mixture of 870 mg (3.0 mmol) of the azetidinium salt and 750 mg (5.0 mmol) of sodium iodide in 60 ml of acetone was heated under reflux with stirring for 22 hr. The acetone was then removed *in vacuo*, and the residual mixture was treated with 6% aqueous sodium hydroxide and extracted with ether. The combined extracts were dried over anhydrous potassium carbonate and evaporated to yield 562 mg (99%) of **N-methyl-N-(3-methyl-3-buten-1-yl)benzylamine (29)**, identified by its nmr spectrum (in $CDCl_3$).

4,5,5-Trimethyl-Δ^1-pyrroline 1-Oxide (30a) and 5,5-Dimethyl-Δ^1-pyrroline 1-Oxide (30b).—The procedure of Bonnett, *et al.*,[33] involving reductive cyclization of the corresponding γ-nitroaldehydes, was employed. These nitrones were stored at 5° under nitrogen to minimize decomposition.

General Procedure for the Formation of Nitrone–Azetidinium Salt Adducts.—1-Benzyl-1,2,2-trimethylazetidinium perchlorate (**3**) was added in portions to an excess of nitrone, and the two reactants were mixed as thoroughly as possible. There was no perceptible heat evolved during this mixing. The reaction was allowed to proceed for 9 days at room temperature with periodic shaking. At the end of this time, the azetidinium salt had dissolved completely. The mixture was then heated at 60° for 12 hr to push the reaction to completion. Treatment with excess ethyl acetate precipitated the adduct in a form sufficiently pure for most purposes.

A mixture of 2.90 g (10.0 mmol) of the azetidinium salt and 10.2 g (80.5 mmol) of 4,5,5-trimethyl-Δ^1-pyrroline-1-oxide (**30a**) yielded 2.05 g (49%) of **6-benzyl-3,3,6,9,10,10-hexamethyl-2-oxa-1-aza-6-azoniabicyclo[5.3.0]decane perchlorate (31a)**. The analytical sample, colorless needles from isopropyl alcohol, had mp 164.0–164.5°; no infrared maxima corresponding to O–H or N$^+$–H; nmr (in $CDCl_3$), at τ 2.52 (s, C_6H_5), 5.46 (s, $ArCH_2$–N$^+$), 5.62 (partially hidden unresolved multiplet, N–CH–N$^+$), 6.51 (m, CH_2CH_2–N$^+$), 6.91 (s, CH_3–N$^+$), 7.3–8.5 (several multiplets, CH_2CH_2–N$^+$ and CH_3–CH–CH_2), 8.7–9.2 (several signals, $(CH_3)_2C$–O, $(CH_3)_2C$–N, and CH_3–CH).

Anal. Calcd for $C_{20}H_{33}ClN_2O_5$: C, 57.61; H, 7.98; N, 6.72. Found: C, 57.68; H, 8.14; N, 6.87.

From 1.45 g (5.0 mmol) of the azetidinium perchlorate and 4.52 g (40.0 mmol) of 5,5-dimethyl-Δ^1-pyrroline-1-oxide (**30b**) there was obtained 0.83 g (41%) of **6-benzyl-3,3,6,10,10-pentamethyl-2-oxa-1-aza-6-azoniabicyclo[5.3.0]decane perchlorate (31b)**. An analytical sample, colorless needles from isopropyl alcohol, had mp 157–158° dec; no O–H or N$^+$–H bands in the infrared spectrum; nmr (in $CDCl_3$), at τ 2.53 (s, C_6H_5), 5.47 (s, $ArCH_2$–N$^+$), 5.61 (partially hidden unresolved multiplet, N–CH–N$^+$), 6.51 (m, CH_2CH_2–N$^+$), 6.93 (s, CH_3–N$^+$), 7.5–8.6 (several multiplets, CH_2CH_2–N$^+$ and C–CH_2CH_2–C), 8.80 and 8.93 (s, s, $(CH_3)_2C$–O and $(CH_3)_2C$–N).

Anal. Calcd for $C_{19}H_{31}ClN_2O_5$: C, 56.63; H, 7.75; N, 6.95. Found: C, 56.80; H, 7.59; N, 6.75.

Lithium Aluminum Hydride Reduction of Adduct 31a.—To a stirred slurry of 380 mg (10.0 mmol) of lithium aluminum hydride in 25 ml of 1,2-dimethoxyethane was added 1.25 g (3.0 mmol) of adduct **31a**. The mixture was heated under reflux for 26 hr and was treated subsequently with 0.76 ml of water and 0.61 ml of 10% aqueous sodium hydroxide. The salts thus precipitated were filtered and washed with hot solvent. The filtrate was then acidified with aqueous hydrochloric acid and evaporated *in vacuo*. Treatment of the residue with 25% aqueous sodium hydroxide liberated a free amine which was extracted into ether. The combined extracts were dried over anhydrous potassium carbonate and evaporated *in vacuo* to yield 926 mg (97%) of **N-methyl-N-[3-methyl-3-(2′,2′,3′-trimethylpyrrolidin-1′-oxy)butyl]benzylamine (32a)** as a yellow oil: no O–H or N–H bands in the infrared spectrum; nmr (in $CDCl_3$), at τ 2.70 (s, C_6H_5), 6.50 (s, $ArCH_2$–N), 6.7–7.3 (unresolved multiplet, CH_2–N–O), 7.3–7.7 (m, CH_2–N(CH_3)–CH_2Ar), 7.81 (s, CH_3–N), 8.1–8.6 (m, $(CH_3)_2$–C–CH_2 and CH_3–CH–CH_2), 8.85 (s, $(CH_3)_2C$–O), 8.98 and 9.20 (s, s, $(CH_3)_2C$–N), 9.12 (partially hidden doublet, J = 6.5 cps, CH_3–CH).

Zinc–Acetic Acid Reduction of 32a.—Activated zinc dust[39] (5.0 g, 77 mg-atoms) was added in portions to a solution of 913 mg (2.9 mmol) of **32a** in 30 ml of 50% aqueous acetic acid. The resulting mixture was then heated at 100° with vigorous stirring for 50 hr. At the end of this time, the residual zinc dust was filtered and washed with water. The filtrate was acidified with 3 ml of concentrated hydrochloric acid and was evaporated *in vacuo*. Upon treatment of the residue with excess 25% aqueous sodium hydroxide, an amine mixture was liberated. This was extracted into ether and the combined extracts were dried over anhydrous potassium carbonate. The ether was then removed by slow distillation through a 6-in. Vigreux column. Glpc analysis (80–200°) of the residual liquid demonstrated the presence of two major components, the retention times of which were found to be identical with those of authentic **2,2,3-trimethylpyrrolidine (33)** and **4-(N-benzyl-N-methylamino)-2-methyl-2-butanol (34)**. Integration of the glpc trace indicated that the yields of the trimethylpyrrolidine and the amino alcohol were 94% and quantitative, respectively.[40] Small samples of both components were collected (70–200°). The infrared and nmr spectra of these compounds proved to be identical in all respects with those of authentic **33** and **34**.

2,2,3-Trimethylpyrrolidine (33) was prepared as described previously[1] by deoxygenation of nitrone **30a** with triphenylphosphine followed by lithium aluminum hydride reduction of the intermediate 4,5,5-trimethyl-Δ^1-pyrroline.

Methyl 3-(N-Benzyl-N-methylamino)propionate (35).—A solution of 34.4 g (0.40 mol) of methyl acrylate and 52.0 g (0.43 mol) of benzylmethylamine in 150 ml of methanol was allowed to stand at room temperature for 9 days. The methanol was then removed *in vacuo* and the residue was distilled to yield 77.2 g (93%) of the amino ester as a clear colorless liquid: bp 73–75° (0.001 mm); ν_{max}^{film} 1745 cm^{-1} (C=O); nmr (in $CDCl_3$), at τ 2.75 (s, C_6H_5), 6.40 (s, CH_3–O), 6.54 (s, $ArCH_2$–N), 7.41 (A_2B_2 system, C–CH_2CH_2–N), 7.85 (s, CH_3–N).

Anal. Calcd for $C_{12}N_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.57; H, 8.35; N, 6.90.

4-(N-Benzyl-N-methylamino)-2-methyl-2-butanol (34).—To 7.3 g (0.30 g-atom) of magnesium turnings under nitrogen was added a small portion of a solution of 45.5 g (0.32 mol) of methyl iodide in 150 ml of ether. As soon as a turbidity began to develop, stirring was started, and the initial vigorous reaction was moderated by cooling in an ice bath. The remainder of the methyl iodide solution was then added dropwise at a rate such that gentle reflux was maintained. The resulting solution was treated with an additional 50 ml of ether and was stirred for 1 hr at room temperature. A solution of 10.4 g (0.05 mol) of methyl 3-(N-benzyl-N-methylamino)propionate (**35**) in 100 ml of ether was then added dropwise with stirring. Following this addition, the mixture was heated under reflux for 5 hr. Work-up was effected by cooling the mixture in an ice bath and adding saturated aqueous ammonium chloride dropwise with stirring until the precipitate of magnesium salts became granular. The precipitate was filtered and washed thoroughly with ether. The filtrate was then dried over anhydrous potassium carbonate and evaporated *in vacuo*. Distillation of the residue through a 12-in. spinning-band column afforded 2.36 g (23%) of the amino alcohol as a clear colorless oil: bp 66–67° (0.025 mm); ν_{max}^{film} 3350 (broad, O–H), 1167 cm^{-1} (C–O); nmr (in $CDCl_3$), at τ 2.72 (s, C_6H_5), 4.12 (s, OH), 6.50 (s, ACH_2–N), 7.32 and 8.38 (A_2X_2 system, C–CH_2CH_2–N), 7.79 (s, CH_3–N), 8.86 (s, $(CH_3)_2$C–O).

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.20; H, 10.22; N, 6.96.

(39) Fischer reagent grade zinc dust was treated successively with 2% aqueous hydrochloric acid, water, 95% ethanol, and ether. The metal thus activated was dried and stored in a vacuum desiccator.

(40) An integrated glpc trace was also obtained for a known mixture of authentic **33** and **34** so as to correct for the difference in detector response toward the two components.

Some Reactions of Methylpyrazines with Organolithium Reagents

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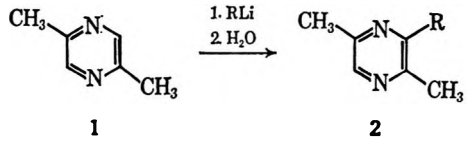
Reactions of isomeric dimethylpyrazines and trimethylpyrazine with methyllithium were studied in some detail. Evidence was found for hydropyrazine intermediates in the ring methylation of 2,5-dimethylpyrazine (**1**). Metalation of the side chain of **1** was observed, as well as ring methylation. In ether solvent vicinally dimethylated pyrazines gave products resulting exclusively from side-chain metalation. Subsequent alkylation and carbethoxylation of these metalated species gave low to moderate yields of side-chain-extended products. In hexane and benzene solvents 2,3-dimethylpyrazine underwent partial ring alkylation with ethyllithium and *n*-butyllithium to form trialkylpyrazines.

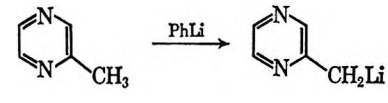
Methyl-substituted pyrazines react with organolithium reagents to form products resulting from ring alkylation (or arylation) and side-chain metalation.

Examples of ring alkylation were first reported by Spoerri[1,2] who found that 2,5-dimethylpyrazine (**1**) reacted to form 3-alkyl-2,5-dimethylpyrazines (**2**) (eq 1).



1 **2** (1)

In the metalation reaction organolithium reagents attack the side chain of a methylpyrazine to form the corresponding pyrazylmethyllithium. Thus Levine[3] found that methylpyrazine (**3**) reacted with phenyllithium to produce pyrazylmethyllithium (**4**) (eq 2),



3 **4** (2)

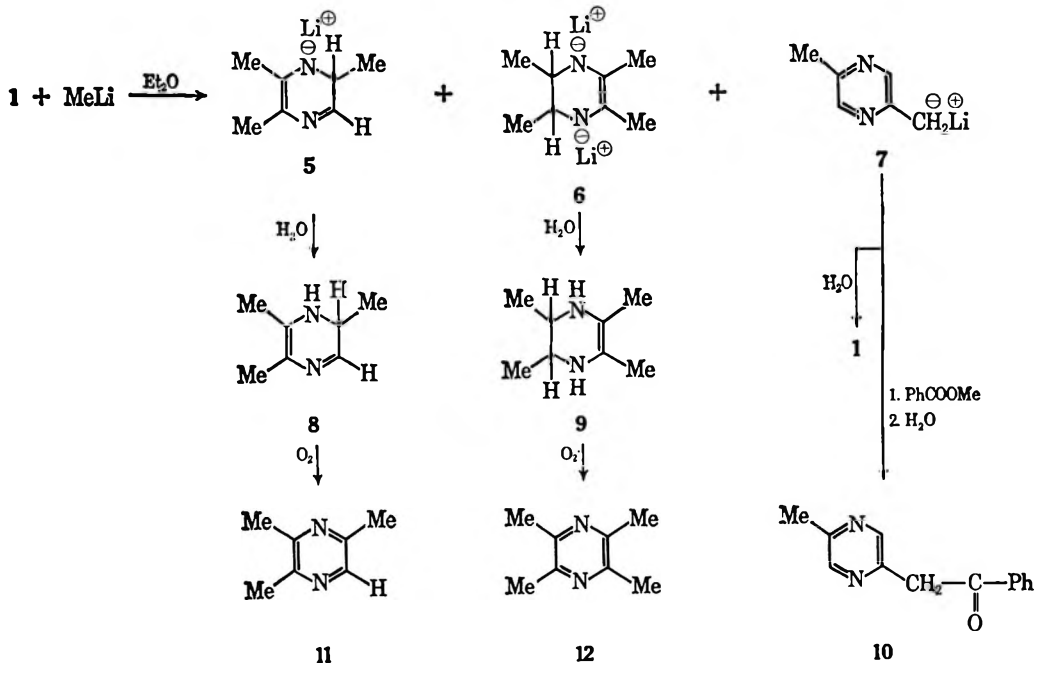
instead of products resulting from ring phenylation.

In contrast to the result obtained with **3**, no successful attempt to metalate the side chain of a dimethylpyrazine or trimethylpyrazine with an organolithium reagent has been reported. In fact it was only very recently that a monolithio derivative of tetramethylpyrazine was prepared.[4]

In the present study we investigated some reactions of dimethylpyrazines and trimethylpyrazine with organolithium reagents in order to learn more about the mechanism of ring alkylation, and also to gain further insight into factors involved in the competition between ring alkylation and side-chain metalation reactions.

(1) B. Klein and P. E. Spoerri, *J. Amer. Chem. Soc.*, **72**, 1844 (1950).
(2) B. Klein and P. E. Spoerri, *ibid.*, **73**, 2949 (1951).
(3) J. D. Behun and R. Levine, *ibid.*, **81**, 5157 (1959).
(4) S. K. Chakrabartty and R. Levine, *J. Heterocycl. Chem.*, **1**, 196 (1964).

SCHEME I



Results

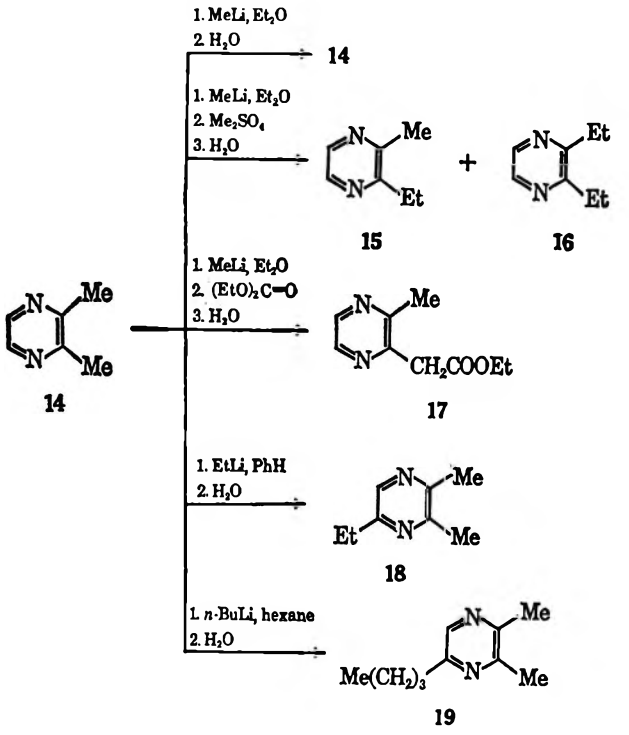
Evidence for Hydropyrazine Intermediates in the Ring Alkylation of Methylpyrazines.—The methylation of 2,5-dimethylpyrazine (**1**) with methyllithium was reinvestigated and the reactions involved are shown in Scheme I. Addition of 1 molar equiv of **1** to ethereal methyllithium at 0° yielded a solid red adduct which was hydrolyzed with water to form trimethylpyrazine (**11**) in 31% yield together with 4.5% of a previously undetected reaction product, tetramethylpyrazine (**12**). A quantity (18%) of **1** was recovered unchanged. In a separate experiment it was shown that **1**, **11**, and **12** were indeed products resulting from hydrolysis of the solid adduct since only traces of pyrazines could be detected when the solid was removed by filtration prior to the water addition step. Also, a low yield of gaseous products was observed during hydrolysis (*ca.* 0.05 mol of gas/mol of methyllithium used), which precluded the presence of any significant amount of free or complexed lithium hydride. These observations did not agree with previously postulated hydride elimination mechanisms,[1,5] but instead they suggested that the initially formed red precipitate was probably a mixture of the adducts **5** and **6** and possibly a methyl-metalated species **7**. Hydrolysis of **5** and **6** should have yielded the 1,2-dihydropyrazine (**8**) and the 1,2,3,4-tetrahydropyrazine (**9**). Indeed, infrared analysis of a crude, hydrolyzed reaction mixture known to contain **1**, **11**, and **12** showed absorptions in regions not attributable to fully aromatic pyrazine species [5.98 and 6.07 (C=N) and 2.88 μ (broad NH)]. Similar absorption maxima were observed by Cornforth[6] who interpreted them as being characteristic of 1,2-dihydropyrazines. We concluded that dihydropyrazines and tetrahydropyrazines were probably formed as transient intermediates during the alkylation of methylpyrazines and that subsequent oxidation of these labile species[7] with atmospheric oxygen during work-up yielded the isolable alkylmethylpyrazines. Additions of organolithium compounds to pyridine[8] and phthalazines[9] have been shown to proceed *via* similar hydroaromatic intermediates, and the instability of these partially reduced aromatic systems toward oxidation is well known. Several attempts to trap the fugitive intermediates **8** and **9** by treating initial methyllithium reaction products with dimethyl sulfate and methyl benzoate were not successful. The result obtained with dimethyl sulfate was understandable since an N-methylated homolog of **8** which was prepared earlier by Karrer[10] was shown to be rather sensitive to chemical manipulation.

The tetramethylpyrazine (**12**) observed in the reaction of **1** and methyllithium was probably formed *via* the bis adduct **6**, (presumably formed by further attack of methyllithium on **5**) since it was found that **11** could not be converted into **12** with methyllithium under similar reaction conditions. In fact, addition of pure **11** to an ethereal solution of methyllithium led only to side-chain metalation (see below) with complete recovery of starting material after hydrolysis. The proposed intermediate tetrahydropyrazine **9** would readily yield **12** during work-up by air oxidation.[11]

The reaction of 2,6-dimethylpyrazine (**13**) with methyllithium appeared to take a similar course to that observed for the 2,5 isomer **1**.[12] In this case addition of 1 molar equiv of **13** to ethereal methyllithium gave, after hydrolysis, a 7% yield of **11** plus 51% recovered **13**. In the case of **13**, no **12** could be detected in the crude reaction product.

(5) M. E. Strem, *Dissertation Abstr.*, **26**, 1355 (1965).
(6) J. W. Cornforth, *J. Chem. Soc.*, 1174 (1958).
(7) The great facility of dihydropyrazines to undergo oxidation with atmospheric O_2 to form pyrazines is well known; *cf.* Y. T. Pratt in "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 408.
(8) K. Ziegler and H. Zeiser, *Chem. Ber.*, **63**, 1847 (1930).
(9) A. Hirsch and D. G. Orphanos, *J. Heterocycl. Chem.*, **3**, 38 (1966).
(10) P. Karrer, T. Isii, F. W. Kahnt, and J. van Bergen, *Helv. Chim. Acta*, **21**, 1174 (1938).
(11) H. I. X. Mager and W. Berends, *Rec. Trav. Chim.*, **84**, 314 (1965).
(12) Compound **13** has been successfully metalated with sodium amide in liquid NH_3; *cf.* R. Levine and coworkers, *J. Org. Chem.*, **29**, 191 (1964), and earlier papers.

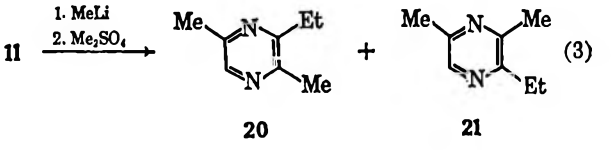
SCHEME II



Metalation of 2,5-Dimethylpyrazine with Methyllithium.—The presence of a methyl metalated species **7** in the initial reaction mixture of 2,5-dimethylpyrazine (**1**) and methyllithium was established by trapping it with methyl benzoate. The initial red adduct of **1** and methyllithium was treated with methyl benzoate *in situ* at 0°. In this way there was obtained a 14% yield of 2-methyl-5-phenacylpyrazine (**10**) which was identical with the authentic ketone prepared by the method of Strem.[5] Since it is known that pyrazylmethyllithium reagents are benzoylated with methyl benzoate,[4] it was concluded that methyl metalation had taken place during the reaction of **1** with methyllithium, and that the extent of metalation was probably in the order of 20%.

Reactions of 2,3-Dimethylpyrazine (14) and Trimethylpyrazine (11) with Organolithium Reagents.—Reactions involving **14** are shown in Scheme II. The addition of **14** to ethereal methyllithium at 0° afforded an insoluble red precipitate, apparently similar to those formed from **1** and **13**, but its formation was accompanied by an evolution of a gas (71% yield, presumed to be methane). Subsequent hydrolysis led only to the recovery of **14**; no trace of **11** could be detected. These results suggested that metalation of **14** had occurred to the complete exclusion of azomethine addition. Attempts to alkylate the ring with methyllithium and ethyllithium in ether under more forcing conditions (*i.e.*, excess reagent at *ca.* 25°) still did not yield trialkylpyrazines, but rather resulted in decomposition of starting materials to unidentified tarry products. The presence of methyl-metalated species in the original reaction mixture was confirmed by treating the red precipitate with dimethyl sulfate. As a result side-chain alkylation took place to form 2-ethyl-3-methylpyrazine (**15**) and 2,3-diethylpyrazine (**16**) in 39 and 10% yields, respectively. Similar reaction of the red precipitate with diethyl carbonate produced 2-carbethoxymethyl-3-methylpyrazine (**17**) in 17% yield. When the metalation reactions were attempted in benzene or hexane solvent some ring alkylation did occur. Thus reactions of **14** with ethyllithium and *n*-butyllithium, respectively, produced 2,3-dimethyl-5-ethylpyrazine (**18**) and 2-*n*-butyl-5,6-dimethylpyrazine (**19**) in 6 and 8% yields.

As mentioned previously trimethylpyrazine (**11**) and methyllithium did not react to yield tetramethylpyrazine (**12**) but instead methyl metalation was the only reaction observed. In this case treatment of the initially formed lithium derivatives with dimethyl sulfate produced 2,5-dimethyl-3-ethylpyrazine (**20**) and 2,6-dimethyl-3-ethylpyrazine (**21**) each in 4% yield together with 27% recovered **11** (eq 3). No trace



(3)

of **18** was observed in the crude reaction product. The reason for the observed solvent effect in reactions of **14** with ethyllithium is still not clear. It is possible that the smaller steric requirement of a presumably monomeric, unsolvated lithium reagent compared with the same reagent in ether, would favor its adding across the pyrazine–azomethine linkage.

Experimental Section

Reactions involving organometallic compounds were carried out in an atmosphere of predried nitrogen. Gas chromatographic analyses and preparative separations of alkylpyrazines were accomplished using a 20 ft × 0.25 in. stainless steel column packed with 18% DEGS on 60–80 mesh, silanized, acid-washed Chromosorb W, and a 10 ft × 0.25 in. stainless steel column packed with 15% SF-96 on a similar support. Nominal column temperatures ranged from 100–150° and the flow rate of carrier gas (He) was 50 ml/min. The first-mentioned column was more effective for resolving isomeric alkylpyrazines. Infrared spectra were obtained on CS_2 solutions unless otherwise specified using

a Perkin-Elmer Model 137 "Infracord" spectrophotometer. Nmr spectra were determined with a Varian HA-100 instrument. Samples were run as 5–10% solutions in CCl_4 and chemical shifts observed at 100 MHz are expressed in τ units relative to tetramethylsilane (internal standard). Multiplicity is indicated by letters in parentheses where s = singlet, d = doublet, t = triplet, q = quartet, and m = complex, unresolved multiplet. Melting points were observed in open capillaries and are uncorrected. Microanalyses were performed by Mr. T. Atanovich and associates of these laboratories and by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Samples of methylpyrazine, 2,5-dimethylpyrazine, 2,6-dimethylpyrazine, and tetramethylpyrazine were obtained commercially and the first three named were distilled from CaH_2 prior to use.

Reactions of 2,5-Dimethylpyrazine (1) with Methyllithium (MeLi). A. Ring Methylation.—The procedure of Spoerri[1] was repeated with slight modification. A stirred, ice-cold solution of MeLi in ether (125 ml of 1.62 *M* MeLi reagent, Alpha Inorganics, Inc.) was treated dropwise with a solution of 2,5-dimethylpyrazine (1) (21.6 g, 0.20 mol) in 25 ml of ether. The dark red solid which formed was stirred vigorously for 10 min at 0° and for 30 min at 25° and finally was cooled again to 0°. Water was added to decompose the red precipitate, and organic products were isolated by continuous ether extraction (16 hr). Distillation of the crude product afforded 13.76 g of a pale orange oil, bp 35–83° (35 mm), which was shown by glpc and infrared analysis to consist of 1 (18% recovery), trimethylpyrazine (11) (31% yield), and tetramethylpyrazine (12) (4.5% yield). In a similar experiment (run on 0.02-mol scale) the initially formed red solid was removed from the reaction mixture by filtration prior to aqueous hydrolysis. The resulting clear filtrate was washed with saturated brine and dried over $MgSO_4$. Evaporation of the filtered ether solution afforded 0.074 g of 11 (0.03% yield). In another experiment (run on 0.00167-mol scale) an attempt was made to measure gas evolution during hydrolysis of the MeLi adduct at 0°. Thus, addition of 1 ml of water led to the evolution of 3.4 ml of gas (collected over water at 26.5° and 745 mm). Under these conditions 0.00167 mol of H_2 would have occupied 44.8 ml.[13]

B. Side-Chain Metalation.—A stirred, ice-cold solution of 1 (8.64 g, 0.080 mol) in 80 ml of ether was treated dropwise with 50.0 ml of 1.62 *M* ethereal MeLi (0.081 mol) over *ca.* 10 min. Then, at 0°, a solution containing 10.87 g (0.080 mol) of freshly distilled methyl benzoate in 40 ml of ether was added and stirring was continued for 1 hr. After standing 2 hr at 25° the reaction mixture was worked up with water and ether as described in part A (above) to yield 17.9 g of a dark, viscous oil. The crude product was chromatographed over silica (60–90 mesh Florex) using benzene and increasing amounts of ether in benzene as eluting solvents. Elution with 2–10% ether afforded 14% of 10 which, after two recrystallizations from 95:5 ethanol–methanol, had mp 104.5–106.5°.

Anal. Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.3; H, 5.3; N, 13.2.

The **2,4-dinitrophenylhydrazone** was obtained in the form of yellow-orange needles from methanol, mp 215–218.5°.

Anal. Calcd for $C_{19}H_{16}N_6O_4$: C, 58.16; H, 4.11; N, 21.42. Found: C, 58.3; H, 4.3; N, 21.4.

The infrared (CH_2Cl_2 and CS_2 solution) and nmr spectra of 10 were identical with those of the authentic ketone,[5] and a mixture melting point of the two substances was not depressed.

Reaction of 2,6-Dimethylpyrazine (13) with MeLi.—Addition of 2.16 g (0.020 mol) of 13 to 1 molar equiv of ethereal MeLi in the manner described for 1 (above) yielded, after work-up and distillation, 1.29 g of volatile products, bp 52–80° (10 mm). Glpc analysis indicated a 7% yield of 11 plus 51% recovered 13.

Reactions of 2,3-Dimethylpyrazine (14) with MeLi. A. Ring Methylation Attempts.—An ether solution containing 3.51 g (0.0325 mol) of 14 was added to an equivalent amount of ethereal MeLi in the manner described for 1 (above). Decomposition of the initially formed red solid with water followed by ether extraction yielded 3.28 g (94%) of crude 14. Short-path distillation of this material afforded 2.85 g (81%) of glpc pure 14, bp 52–60° (12 mm).

Glpc analysis of the crude product showed only a trace of 11. Similar experiments carried out with a large (~tenfold) molar excess of MeLi or EtLi at 25° also led only to 14.

(13) Corrected for the solubility of H_2 in ether at 0°.

B. Side-Chain Metalation.—A flask arranged for collection of evolved gases was charged with 10.0 ml of 1.62 *M* ethereal MeLi and stirred at 0°. Dropwise addition of 1.71 ml (0.0162 mol) of anhydrous 14 to the MeLi solution led to immediate gas evolution (0.0112 mol) and concomitant precipitation of a deep red solid. The red precipitate was treated dropwise with a solution of freshly distilled dimethyl sulfate (1.51 ml, 0.0162 mol) in 5 ml of ether. After 30 min at 0° and 2 hr at 25° water was added; the mixture was worked up as described in A to give 1.64 g of yellow oil. Distillation gave 1.27 g of distillate, bp 63–88° (16 mm). Glpc analysis indicated three compounds which were isolated (preparative glpc) and identified as 14, 2-ethyl-3-methylpyrazine (15), and 2,3-diethylpyrazine (16) by their nmr and infrared spectra. The glpc yields of 15 and 16 were 39 and 10%, respectively. Recovery of 14 was 15%.

C. Carbethoxylation of Metalated 14 with Diethyl Carbonate.—The metalation reaction described in part B was repeated on a 0.02-mol scale. The red suspension was stirred at 0° while a solution of diethyl carbonate (1.21 ml, 0.010 mol) in 5 ml of ether was added dropwise over 5 min. After stirring 30 min at 0° and 2 hr at 25°, the mixture was decomposed with water and extracted with ether. Distillation of the crude product obtained after concentration of the dried ($MgSO_4$) ether solution yielded 1.58 g of an oil, bp 64–157° (27 mm), which was shown by glpc analysis to contain 14 (32% recovery) and 2-carbethoxymethyl-3-methylpyrazine (17) (17% yield). Compound 17 was isolated by preparative glpc as a clear, pale yellow oil.

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.9; H, 6.8; N, 15.6.

The infrared spectrum showed characteristic ester absorption at 5.75 μ. Nmr analysis showed peaks at τ 1.78 (m, ring protons, 2 H), 5.90 (q, $CH_2C<$, 2 H), 6.27 (s, $-CH_2-$, 2 H), 7.51 (s, ring methyl, 3 H), 8.74 (t, $CH_3C<$, 3 H).

Reactions of Trimethylpyrazine (11) with MeLi.—To a stirred, ice-cold mixture of 3.0 ml of 1.62 *M* ethereal MeLi and 3.0 ml of ether was added a solution containing 0.237 g (0.00194 mol) of glpc pure 11 in 2 ml of ether. After 2 hr at 0°, water (2 ml) was added, and the mixture was extracted with ether. Concentration of the dried ($MgSO_4$) ether solution afforded 100% recovery of 11. No 12 could be detected in the crude product by glpc. A similar reaction mixture prepared from 0.253 g (0.0021 mol) of 11 and an equivalent amount of MeLi was treated dropwise with 0.20 ml (0.0021 mol) of dimethyl sulfate in a few milliliters of ether. Addition of water followed by ether work-up yielded 0.235 g of crude product. Evaporative distillation at 80–160° (15 mm) afforded 0.117 g of a yellow oil which was resolved into three components by preparative glpc. The compounds identified (infrared spectra and glpc retention times) were 11, 2,5-dimethyl-3-ethylpyrazine[2,14] (20), and 2,6-dimethyl-3-ethylpyrazine[14] (21). Materials 20 and 21 were obtained in 4 and 6% yields, respectively, together with 27% of recovered 11.

2,3-Dimethylpyrazine (14).—To 64.0 g (0.582 mol) of 2,3-dimethyl-5,6-dihydropyrazine[15] contained in a 3-l., round-bottomed flask were added 1200 ml of 33% aqueous KOH solution and 320 g of reagent-grade $HgCl_2$. After heating and stirring 2.5 hr on a steam bath, the flask was arranged for steam distillation, and 1 l. of aqueous distillate was collected. Continuous ether extraction (16 hr) followed by distillation afforded 17.6 g (28%) of 14, bp 156–158°, picrate derivative, mp 151–153° (lit.[16] bp 156°, picrate mp 150°).

2-Ethyl-3-methylpyrazine (15).—Compound 15 was prepared in a manner similar to 14. Thus 59.0 g (0.476 mol) of 2-ethyl-3-methyl-5,6-dihydropyrazine (prepared from 2,3-pentanedione and ethylenediamine by the method reported for the synthesis of the 2,3-dimethyl homolog)[15] was oxidized with $HgCl_2$ to yield, after distillation, 9.8 g (17%) of 15: bp 69–70° (16 mm); nmr, τ 1.88 (m, ring protons, 2 H), 7.57 (s, ring CH_3, 3 H), 7.28 (q, CH_2, 2 H), 8.77 (t, chain CH_3, 3 H).

Anal. Calcd for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.9; H, 8.5; N, 22.5.

2,3-Diethylpyrazine (16).—The pyrazine 16 was prepared by the method outlined for 14 and 15 starting with 3,4-hexanedione[17] and ethylenediamine. The over-all yield of steam distilled, glpc pure 16 was 15%. A sample of the oily product was purified for

(14) G. P. Rizzi, *J. Agr. Food Chem.*, **15**, 549 (1967).

(15) T. Ishiguro and M. Matsumura, *Yakugaku Zasshi*, **78**, 229 (1958); *Chem. Abstr.*, **52**, 11862 (1958).

(16) Beilstein, "Handbook of Organic Chemistry," Vol. 23, Springer-Verlag, Berlin, 1936, p 95.

(17) W. Rigby, *J. Chem. Soc.*, 793 (1951).

analysis by preparative glpc. Nmr analysis gave peaks at τ 1.84 (s, ring protons, 2 H), 7.24 (q, CH_2, 4 H), 8.75 (t, chain CH_3, 6 H).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.7; H, 8.9; N, 20.7.

2,3-Dimethyl-5-ethylpyrazine (18).—A 50-ml portion of 2.22 *M* ethyllithium in benzene (0.111 mol, Alpha Inorganics, Inc.) was stirred and cooled to 10° while a solution of **14** (2.17 g, 0.020 mol) in benzene (10 ml) was added dropwise. The dark red slurry which formed was stirred 0.5 hr at 0° and 21.5 hr at 25°. After recooling to 0°, water was admitted and organic products were extracted with ether. Short-path distillation yielded 0.548 g of pale yellow oil, bp 60–102° (15 mm). Analysis of this oil by glpc indicated two major products, recovered **14** and 2,3-dimethyl-5-ethylpyrazine. The glpc yields of **14** and **18** were 18 and 6%, respectively. An analytical specimen of **18** was isolated by preparative glpc and further purified by evaporative distillation. Nmr analysis gave peaks at τ 2.03 (s, ring proton, 1 H), 7.61 (s, ring methyls, 6 H), 7.36 (q, CH_2, 2 H), 8.76 (t, ethyl CH_3, 3 H).

Anal. Calcd for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57. Found: C, 70.6; H, 8.9; N, 20.6.

2-*n*-Butyl-5,6-dimethylpyrazine (19).—A mixture containing 10 ml of dry hexane and 20.0 ml (0.032 mol) of 1.6 *M* *n*-butyllithium in hexane (Foote Mineral Co.) was stirred at 0° and treated dropwise (over 10 min) with a solution of **14** (1.74 g, 0.016 mol) in 5 ml of hexane. After stirring 1 hr at 0° and 1 hr at 25°, the reaction mixture was cooled and decomposed with water (10 ml). Ether extraction afforded 1.8 g of crude product which, after short-path distillation, yielded 1.01 g of a yellow oil, bp 59–114° (16 mm). Glpc analysis indicated two oily components which were trapped and identified as **14** and 2-*n*-butyl-5,6-dimethylpyrazine (**19**). Glpc yields of **14** and **19** were 42 and 8%, respectively. A sample of **19** was evaporatively distilled prior to analysis. Nmr analysis gave peaks at τ 2.07 (s, ring proton, 1 H), 7.64 (s, ring methyl, 6 H), 7.42 (t, ring CH_2, 2 H), 9.11 (t, *n*-butyl CH_3, 3 H).

Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82; N, 17.06. Found: C, 72.9; H, 9.8; N, 17.2.

Registry No.—**1**, 123-32-0; **10**, 15707-19-4; **10** 2,4-dinitrophenylhydrazone, 15707-20-7; **11**, 14667-55-1; **13**, 108-50-9; **14**, 5910-89-4; **15**, 15707-23-0; **16**, 15707-24-1; **17**, 15707-25-2; **18**, 15707-34-3; **19**, 15834-78-3.

Acknowledgment.—The author gratefully acknowledges helpful suggestions provided by Drs. N. R. Artman, W. F. Erman, and C. D. Broaddus. Credit is also due Mr. Norvin Gullion, who performed some of the experimental work described.

Synthesis of a Pyridoxal Analog, 4,5-Diformyl-3-hydroxy-2-methylpyridine[1a]

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A route for the synthesis of the compound 4,5-diformyl-3-hydroxy-2-methylpyridine (X) (an analog of pyridoxal) is described. The key intermediate in this synthesis was the previously undescribed dimethyl acetal of isopyridoxal (VI) which was synthesized from the corresponding acetylated diethyl mercaptal (V) by demercaptalation in methanol using mercuric chloride and mercuric oxide. For the removal of the mercuric chloride, ammonium hydroxide has been found to be the most suitable reagent. Oxidation of the 4-hydroxymethyl group of this intermediate (VI) with manganese dioxide "B" and acid hydrolysis of the product of oxidation gave the desired dialdehyde X which has been shown to exist in a hydrated form as a dihemiacetal. Derivatives like the bismethoxyoxime (XI) and bisthiosemicarbazone (XII) were prepared. Reduction of the *o*-dialdehyde X with sodium borohydride gave pyridoxol.

In the course of investigations concerning the biosynthetic pathway of vitamin B_6 in yeast[2] and its catabolism in rats,[3,4] we have isolated compounds, related to this vitamin, that showed growth-promoting activity for *Lactobacillus casei* and/or *Saccharomyces carlsbergensis*. Pyridoxal and isopyridoxal,[5] which have a formyl group in place of the hydroxymethyl group at the 4 or 5 position of the pyridoxol molecule, respectively, are both growth-promoting factors for *Saccharomyces carlsbergensis*.[6,7] Therefore, the compound 4,5-diformyl-3-hydroxy-2-methylpyridine (*o*-pyridoxidial[8]) (X, Scheme I), which has both the 4- and 5-hydroxymethyl groups of the pyridoxol molecule replaced by formyl groups, was needed to be tested as a possible precursor or catabolite of the vitamin. A synthesis of this pyridoxal analog is herein described; its biological properties are under investigation.

Gardner, *et al.*,[9] have described a synthesis of the bisthiosemicarbazone derivative of compound X using a double Sommelet reaction; however, the identity of this product was not conclusively established.[10] A detailed study[10–15] of the Sommelet reaction seems to show no promise for the synthesis of *o*-dialdehydes through a double Sommelet reaction. Ried and Bodem[16] have made many aromatic and heteroaromatic *o*-dialdehydes using vicinal dibromides and N-bromosuccinimide in the presence of peroxides, but this method did not seem to be applicable in the

(1) (a) This investigation was supported by a U. S. Public Health Service Research Grant (AM 00257). (b) To whom inquiries should be addressed.

(2) R. S. Pardini and C. J. Argoudelis, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p C309.

(3) C. J. Argoudelis and F. A. Kummerow, *Biochemistry*, **5**, 1 (1966).

(4) C. J. Argoudelis, unpublished data.

(5) The growth-promoting activity of isopyridoxal is, unquestionably, a result of its conversion into pyridoxol and thence to pyridoxal phosphate: E. E. Snell, *Vitamins Hormones*, **16**, 77 (1958)).

(6) E. E. Snell, *J. Biol. Chem.*, **154**, 313 (1944).

(7) E. E. Snell and A. N. Rannefeld, *ibid.*, **157**, 475 (1945).

(8) Three new pyridine dialdehydes related to vitamin B_6 have been named trivially as *o*-, *m*-, and *p*-pyridoxidial. These dialdehydes have the two formyl groups in the *ortho* (4,5), *meta* (2,4), and *para* (2,5) positions of the pyridoxol molecule, respectively. Syntheses of the *m*- and *p*-pyridoxidials are in progess.

(9) T. S. Gardner, F. A. Smith, E. Wenis, and J. Lee, *J. Org. Chem.*, **16**, 1121 (1951).

(10) S. J. Angyal, *Org. Reactions*, **8**, 197 (1954).

(11) S. A. Harris, D. Heyl, and K. Folkers, *J. Amer. Chem. Soc.*, **66**, 2088 (1944).

(12) S. J. Angyal, P. J. Morris, R. C. Rassac, and J. A. Waterer, *J. Chem. Soc.*, 2704 (1949).

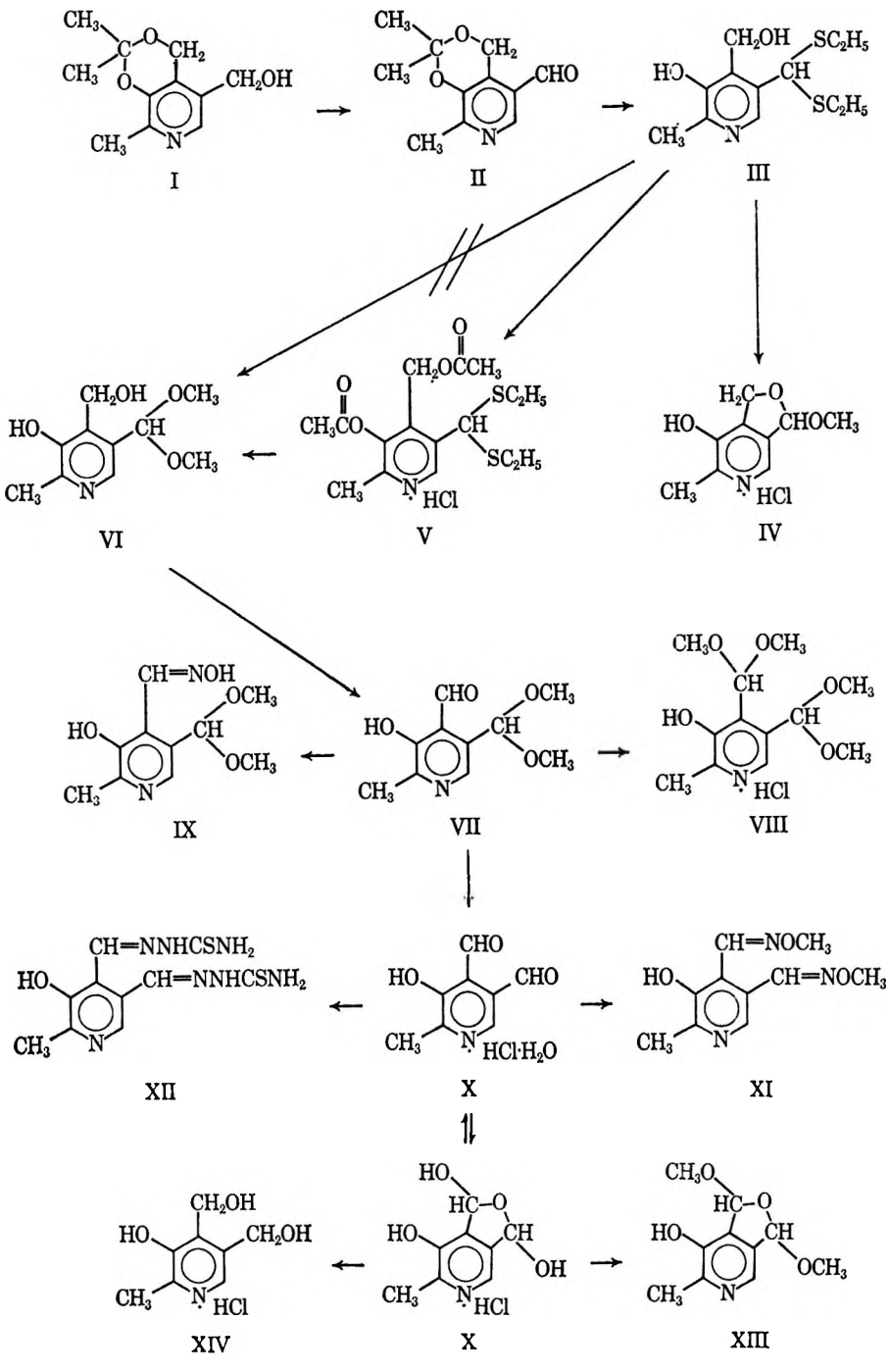
(13) R. C. Fuson and J. J. Denton, *J. Amer. Chem. Soc.*, **63**, 654 (1941).

(14) S. J. Angyal, G. B. Barlin, and P. C. Wailes, *J. Chem. Soc.*, 1740 (1953).

(15) J. H. Wood, C. C. Tung, M. A. Perry, and R. E. Gibson, *J. Amer. Chem. Soc.*, **72**, 2992 (1950).

(16) W. Ried and H. Bodem, *Chem. Ber.*, **89**, 708 (1956); **89**, 2328 (1956).

SCHEME I



present case. Ried[17] has reported that Weygand synthesized pyridine 2,3- and 3,4-dialdehydes by reducing the bis-N-methyl anilides of the corresponding dicarboxylic acids with lithium aluminium hydride; however, no experimental data are available. Paul and Korytnyk[18] reported the synthesis of *o*-pyridoxidial (X) along similar lines, but they also did not furnish any experimental details or physical data.

In the pyridoxol molecule, the 4-hydroxymethyl group is known to be more reactive than the 5-hydroxymethyl group toward oxidizing agents.[11,19] An attempt was therefore made to oxidize with manganese dioxide "B" the 4-hydroxymethyl group of isopyridoxal to obtain the *o*-pyridoxidial (X). Oxidation of benzylic alcohols with manganese dioxide "B" is known to stop at the aldehyde stage;[20] however, in this case 5-pyridoxic acid lactone was isolated. Apparently, the predominating hemiacetal form of isopyridoxal[21] is oxidized preferentially to the open form. Similarly when pyridoxal was oxidized, 4-pyridoxic acid lactone was obtained.

Direct attempts to make the dimethyl or diethyl acetals of isopyridoxal failed, as it exists mainly in the hemiacetal form.[21] Preparation of dimethyl acetals from the corresponding diethyl mercaptals using mer-

(17) W. Ried, *Angew. Chem.*, **67**, 357 (1955).

(18) B. Paul and W. Korytnyk Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, P063.

(19) I. Tomita, H. G. Brooks, and D. E. Metzler, *J. Heterocycl. Chem.*, **3**, 178 (1966).

(20) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

(21) W. Korytnyk, E. J. Kris, and R. P. Singh, *ibid.*, **29**, 574 (1964).

curic chloride and mercuric oxide is a very common reaction in carbohydrate chemistry. This method has not been used in pyridine chemistry since pyridine and some of its derivatives form insoluble salts with mercuric chloride. The diethyl mercaptal of isopyridoxal (III) was obtained in a one-step reaction from isopropylidine isopyridoxal (II) and ethyl mercaptan. The conversion of diethyl mercaptal into dimethyl acetal followed a pattern similar to that observed in the case of carbohydrates.[22,23] In an attempt to convert the diethyl mercaptal III, which has the neighboring hydroxymethyl group free, into the dimethyl acetal VI, the monomethyl acetal IV was formed, but when the neighboring hydroxymethyl group of this mercaptal (III) was esterified (V) it was possible to convert it into the desired dimethyl acetal (VI). The isolation of the acetal VI presented difficulties due to the mercuric chloride which could not be completely removed from the reaction mixture by the usual methods.[24] Concentrated aqueous ammonium hydroxide solution was found to be the most suitable reagent for this purpose; it removed mercuric chloride almost completely from the reaction mixture as an insoluble precipitate of mercuric aminochloride $Hg(NH_2)Cl$. In addition to removing mercuric chloride, it also hydrolyzed the ester groups simultaneously which was quite advantageous in the present case.[25]

With the key intermediate (VI) in hand, the synthesis of the *o*-pyridoxidial (X) was a straightforward process. Oxidation of the 4-hydroxymethyl group with manganese dioxide "B" yielded the aldehyde VII. The aldehyde VII formed an oxime (IX) with hydroxylamine and a bisdimethyl acetal (VIII) with methanol. Acid hydrolysis of the aldehyde VII yielded the desired dialdehyde X. Despite the presence of two formyl groups in the molecule, compound X did not have any carbonyl absorption in its infrared spectrum. It has been reported[26] that pyridine aldehydes have a pronounced tendency (in aqueous media) to form hydrates of the general structure $RCH(OH)_2$. In general, the stronger the electron-attracting power of the neighboring group, the easier is the hydration of the aldehyde.[26,27] As a result of the two formyl groups being *ortho* to each other in *o*-pyridoxidial hydrochloride (X), when one of them is hydrated, it interacts with the other forming a dihemiacetal type of structure which is stable even in the solid state, thereby explaining the lack of a carbonyl band in the infrared spectrum. Absence of carbonyl peaks in the infrared spectrum of pyridoxal[28] and isopyridoxal[21] have similarly been explained on the basis of their existence in the hemiacetal form. Existence of the dialdehyde X as a monohydrate is in agreement with its analytical data. *o*-Pyridoxidial (X) formed a cyclic dimethyl acetal (XIII) with methanol which was very different from the dimethyl acetal VII. Although no crystalline derivative could be isolated by treating the dialdehyde X with hydroxylamine hydrochloride, a bismethoxy oxime (XI) and a bisthiosemicarbazone[29] (XII) were obtained when the dialdehyde X was treated with methoxyamine hydrochloride or thiosemicarbazide, respectively. Formation of the above derivatives indicates that in solution there is an equilibrium between the free dialdehyde and its cyclic dihemiacetal form.

When pyridoxal, isopyridoxal, and the dialdehyde X were reduced with sodium borohydride under similar conditions, pyridoxol was obtained, indicating thereby, that in *o*-pyridoxidial (X) the two formyl groups are present in the 4 and 5 positions of the pyridine ring.

Experimental Section[30]

5-(Hydroxymethyl)-2,2,8-trimethyl-4H-*m*-dioxino[4,5-c]pyridine (isopropylidene pyridoxol) (I) was synthesized by the method of Korytnyk and Wiedeman.[31]

5-Formyl-2,2,8-trimethyl-4H-*m*-dioxino[4,5-*c*]pyridine (isopropylidene isopyridoxal) (II) was prepared by a modification of the method reported by Brooks, *et al.*[32] A mixture of 80 g of manganese dioxide "B" and 20 g of isopropylidene pyridoxol free base in 200 ml of chloroform was stirred at room temperature for 24 hr. The reaction mixture was diluted with 400 ml of chloroform and filtered with suction through a layer of "Celite." The contents of the funnel were washed with five 200-ml portions of boiling chloroform. The combined filtrate and washings were evaporated under reduced pressure to an oily residue to which was added 400 ml of petroleum ether (bp 40–50); it was then warmed and filtered. The filtrate was treated with a small amount of activated charcoal, filtered again, and kept in a refrigerator overnight when crystalline isopropylidene isopyridoxal was obtained. The total yield of the product, mp 62–63° (lit.[32] mp 62–63°), was 17.2 g (86.7%).

5′-(Diethyl mercaptal)-3-hydroxy-4-hydroxymethyl-2-methylpyridine (Isopyridoxal Diethyl Mercaptal) (III).—Isopropylidene isopyridoxal (II) (31.8 g) was dissolved in 150 ml of cold (−5 to −10°) ethyl mercaptan; dry hydrogen chloride gas was passed through the solution for 10 min, taking care to keep the temperature of the reaction mixture below −5°; and the solution was kept in a deep freeze for 24 hr. Excess of mercaptan was removed under reduced pressure; 400 ml of water was added to the residue; and the mixture was left overnight to hydrolyze the isopropylidene ring. This was neutralized with sodium bicarbonate solution and extracted with four 500-ml portions of ether. The ether extract was washed free of alkali, dried over anhydrous sodium sulfate, and concentrated to about 200 ml. Petroleum ether was added until turbidity occurred, and the solution was kept in a refrigerator; 31.8 g of white shining crystals of the mercaptal III, mp 99–100°, was obtained. An additional 6 g of compound III was obtained by concentrating the mother liquor and adding more petroleum ether, making the total yield 37.8 g (90.2%) (recrystallization from diethyl ether–petroleum ether mixture did not change the melting point): $\lambda_{max}^{0.1\ N\ HCl}$ 298 mμ (ε 8.7 × 10³) and 230 (sh) (4.5 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 315 mμ (ε 8.4 × 10³) and 245 (6.2 × 10³).

(22) J. W. Green and E. Pacsu, *J. Amer. Chem. Soc.*, **60**, 2056 (1938).

(23) D. L. MacDonald and H. G. Fletcher, Jr., *ibid.*, **81**, 3719 (1959).

(24) Extraction with solvents such as chloroform [H. R. Bolliger and M. D. Schmid, *Helv. Chim. Acta*, **34**, 1597 (1951)], ether, or methylene chloride,[21] and washing the extract with saturated potassium iodide solution to remove mercuric chloride was a very inefficient process, and mercuric chloride could not be completely removed in this way without losing much of the product. Isolation procedures involving prolonged contact of mercuric chloride with the reaction mixture were unsuitable because mercuric chloride seemed to catalyze the hydrolysis of the dimethyl acetal, resulting in a mixture of products.

(25) When mercuric aminochloride was precipitated by passing anhydrous ammonia gas into the reaction mixture, acetamide was formed which was difficult to separate from the product VI.

(26) K. Nakamoto and A. E. Martell, *J. Amer. Chem. Soc.*, **81**, 5857 (1959); **81**, 5863 (1959).

(27) S. F. Mason, *J. Chem. Soc.*, 5010 (1957).

(28) D. Heinert and A. R. Martell, *J. Amer. Chem. Soc.*, **81**, 3933 (1959).

(29) The bisthiosemicarbazone was extremely hygroscopic, and consequently the analytical data were not in good agreement with the theoretical values. The crude precipitate had a weak carbonyl absorption at 1692 cm^{-1} which disappeared on recrystallization indicating that initially a mixture of mono- and bisthiosemicarbazone was formed.

(30) All melting points are corrected. Microanalyses were carried out by Clark Microanalytical Laboratories, Urbana, Ill. Ultraviolet absorption spectra were determined on a Model 11 M Cary recording spectrophotometer. Infrared spectra were determined in potassium bromide pellets with the aid of a Beckman Model IR-7 recording spectrophotometer.

(31) W. Korytnyk and W. Wiedeman, *J. Chem. Soc.*, 2531 (1962).

(32) H. G. Brooks, Jr., J. W. Laakso, and D. E. Metzler, *J. Heterocycl. Chem.*, **3**, 126 (1966).

Anal. Calcd for $C_{12}H_{19}NO_2S_2$: C, 52.72; H, 7.00; N, 5.12; S, 23.45. Found: C, 52.46; H, 6.68; N, 5.15; S, 23.62.

3-Acetoxy-4-acetoxymethyl-5′-(diethyl mercaptal)-2-methylpyridine Hydrochloride (Isopyridoxal Diethyl Mercaptal 3,4-Diacetate Hydrochloride) (V).—Isopyridoxal mercaptal (III) (30 g), 120 ml of pyridine (freshly distilled over potassium hydroxide), and 50 ml of acetic anhydride were mixed in a round-bottom flask. After standing overnight at room temperature, the reaction mixture was evaporated under vacuum at 80–90° bath temperature. The last traces of pyridine were removed by repeated evaporations with anhydrous ether. The residue was extracted with 300 ml of anhydrous ether and filtered, and dry hydrogen chloride gas passed into the filtrate; crude isopyridoxal mercaptal-3,4-diacetate hydrochloride precipitated. Recrystallization was carried out by dissolving the hydrochloride in ethanol at room temperature, adding ether until turbidity occurred, and refrigerating. The yield obtained was 40.7 g (94%): mp 132–133°; $\lambda_{max}^{0.1\ N\ HCl}$ 274 mμ (ε 6.1 × 10³) and 218 (sh) (6.4 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 315 mμ (ε 8.3 × 10³) and 245 (6.4 × 10³).

Anal. Calcd for $C_{16}H_{23}NO_4S_2 \cdot HCl$: C, 48.78; H, 6.14; N, 3.55; S, 16.27. Found: C, 48.35; H, 6.09; N, 3.58; S, 16.56.

5′-(Dimethyl acetal)-3-hydroxy-4-hydroxymethyl-2-methylpyridine (Isopyridoxal Dimethyl Acetal) (VI).—To a solution of 12 g of the diacetate V in 1200 ml of boiling methanol (dried over magnesium methoxide and iodine)[33] was added 37 g of mercuric oxide and vigorous stirring started. A solution of 35 g of mercuric chloride in 140 ml of methanol was added to the above suspension; the mixture was refluxed with stirring for 30 min and then filtered hot under suction. The residue on the funnel was washed with five 200-ml portions of boiling methanol. The combined filtrate and washings were concentrated to about 750 ml under reduced pressure at 70° bath temperature and cooled and 250 ml of concentrated ammonium hydroxide solution was added to it. The copious white precipitate of mercuric aminochloride was filtered under suction and washed with methanol. The filtrate was filtered once more under gravity in order to remove suspended inorganic salts. The clear filtrate was evaporated under reduced pressure at a bath temperature of 35–45° until a white residue precipitated. The contents of the flask were extracted with ether several times, to the combined ether extracts excess of petroleum ether was added, and this was refrigerated overnight, yielding 5.89 g (89.6%) of dimethyl acetal VI in the form of white needles: mp 167–168° (recrystallization from moist diethyl ether–petroleum ether mixture did not change the melting point); $\lambda_{max}^{0.1\ N\ HCl}$ 291 mμ (ε 10.5 × 10³) and 228 (sh) (3.4 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 309 mμ (ε 8.3 × 10³) and 246 (7.9 × 10³).

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.52; H, 6.87; N, 6.62.

The structure of the dimethyl acetal VI was supported by a negative Gibb's test in the presence of borate buffer,[34] by its ultraviolet spectrum in alkaline solution, which was similar to pyridoxol, and, finally, by its hydrolysis to isopyridoxal with hydrochloric acid.

Starting from isopyridoxal diethyl mercaptal (III) and following a procedure as described in detail for preparing compound VI only a monomethyl acetal (IV) was obtained, which gave a positive 2,6-dichloroquinone chloroimide test in the presence of borate buffer, indicating thereby that the 4-hydroxymethyl group was not free in this compound. The hydrochloride of compound IV was found to be identical with the hydrochloride of the monomethyl acetal of isopyridoxal prepared by the method of Korytnyk, *et al.*,[20] in its melting point and infrared and ultraviolet spectra.

5′-(Dimethyl acetal)-4-formyl-3-hydroxy-2-methylpyridine (VII).—A mixture of 2 g of the dimethyl acetal VI and 8 g of manganese dioxide "B" in 1500 ml of chloroform was stirred with a mechanical stirrer for 5 hr. The suspension was filtered and the solvent removed from the filtrate under reduced pressure at 30–35°. The residue was extracted with petroleum ether, decolorized with activated carbon at room temperature, concentrated to about 10 ml, and kept in a refrigerator. The precipitated compound was recrystallized twice from petroleum ether to yield 1.35 g (68.2%) of aldehyde dimethyl acetal (VII): mp 58–59°; $\lambda_{max}^{0.1\ N\ HCl}$ 337 mμ (ε 1.7 × 10³) and 294 (7.2 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 387 mμ (ε 7.1 × 10³) and 230 (15.1 × 10³).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.70; H, 6.26; N, 6.78.

The structure of compound VII was verified from the fact that its infrared spectrum had a strong sharp carbonyl peak at 1673 cm^{-1} and its ultraviolet spectrum in alkaline medium had an absorption at λ_{max} 387 mμ and no absorption near 300 mμ. These data are in agreement with those reported for aldehydes that cannot form a cyclic hemiacetal (*e.g.*, isopropylidene isopyridoxal,[21] 5-deoxypyridoxal,[35] and pyridoxal-5-phosphate[36]).

4′,5′-Bis(dimethyl acetal)-3-hydroxy-2-methylpyridine Hydrochloride (VIII).—A slow stream of dry hydrogen chloride gas was passed in approximately 20 ml of sodium-dried ether for about 1 min with protection from moisture. This hydrogen chloride–ether solution was added drop by drop to a solution of 210 mg of compound VII in 40 ml of anhydrous ether with constant stirring until precipitation was complete. The precipitated hydrochloride was immediately filtered under suction, washed a few times with anhydrous ether, and dried in a vacuum desiccator over phosphorous pentoxide; 230 mg of a creamy white powder melting at 123–124° dec was obtained. A 200-mg portion of this hydrochloride was dissolved in 50 ml of absolute methanol[33] and refluxed in an oil bath at 70° for 14 hr. Part of the methanol was evaporated, ether was added to the point of turbidity, and the mixture was kept in a refrigerator whereupon impure crystals of compound VIII were obtained. The crystals were suspended in anhydrous ether and dry ammonia gas was passed into it. The precipitated ammonium chloride was filtered off. The filtrate was evaporated to dryness *in vacuo* at 40°; the residue was dissolved in 15 ml of petroleum ether and kept in a refrigerator for about 2 hr. A small amount of white crystalline material precipitated which was filtered off and identified by its melting point and ultraviolet and infrared spectra as the cyclic dimethyl acetal XIII. The filtrate was evaporated under vacuum leaving an oily residue which was carefully converted into the solid hydrochloride VIII as described earlier. The yield was 180 mg (75.8%): mp 149–150° dec; $\lambda_{max}^{0.1\ N\ NaOH}$ 316 mμ (ε 7.9 × 10³) and 247 (7.8 × 10³).[37]

Anal. Calcd for $C_{12}H_{19}NO_5 \cdot HCl$: C, 49.06; H, 6.86; N, 4.77. Found: C, 49.06; H, 6.88; N, 4.69.

5′-(Dimethyl acetal)-4′-oxime-3-hydroxy-2-methylpyridine (IX).—The dimethyl acetal VI (1 g) was oxidized to the aldehyde VII with manganese dioxide "B" in chloroform as described earlier. The petroleum ether extract obtained at the end of the reaction was evaporated to dryness, and 50 ml of 0.1 *N* hydrochloric acid added to it. The reaction mixture was diluted to 200 ml with distilled water and stirred to dissolve all the compound. A solution of 0.53 g of hydroxylamine hydrochloride in 2 ml of water was added; the oxime precipitated immediately. Solid sodium acetate was added to bring the pH to 5–6. After adding some ice crystals to cool the mixture to about 5°, the oxime was filtered under suction to yield 0.821 g (77.4%), mp 195–197° dec. An analytical sample was recrystallized from ethanol–water mixture: no change in the melting point was observed; $\lambda_{max}^{0.1\ N\ HCl}$ 324 mμ (ε 9.4 × 10³) and 272 (10.2 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 332 mμ (ε 8.4 × 10³) and 242 (14.9 × 10³).

Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.98; H, 6.07; N, 11.90.

4,5-Diformyl-3-hydroxy-2-methylpyridine Hydrochloride (*o*-Pyridoxidial Hydrochloride) (X).—The aldehyde dimethyl acetal (VII) (2 g) was heated with 100 ml of 1 *N* hydrochloric acid at 60° (water bath) for 30 min. A small amount of activated carbon was added and the reaction mixture filtered after about 10 min of heating. The filtrate was concentrated to about 1 ml, excess of acetone was added, and the solution was kept in a refrigerator overnight to yield 1.8 g (90%) of crystalline *o*-pyridoxidial hydrochloride (X), which decomposed without melting at 158–161°: $\lambda_{max}^{0.1\ N\ HCl}$ 288 mμ (ε 8.9 × 10³) and 227 (3.5 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 303 mμ (ε 6.2 × 10³) and 243 (6.8 × 10³); $\lambda_{max}^{pH\ 10}$ 394 mμ (ε 1.9 × 10³), 303 (4.8 × 10³), and 243 (8.7 × 10³).[38]

(33) A. I. Vogel in "Practical Organic Chemistry," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1962, p 169.

(34) J. V. Scudi, W. A. Bastedo, and T. J. Webb, *J. Biol. Chem.*, **136**, 399 (1940).

(35) D. Heyl, S. A. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, **75**, 653 (1953).

(36) N. Viscontini, C. Ebnöther, and P. Karrer, *Helv. Chim. Acta*, **34**, 1834 (1951).

(37) The bisdimethyl acetal hydrochloride (VIII) was hydrolyzed almost immediately in 0.1 *N* HCl solution.

(38) When the spectrum at pH 10 (sodium carbonate–sodium bicarbonate buffer) was recorded immediately the absorption was at λ_{max} 400 mμ which shifted toward lower wave lengths with time. The extinction coefficient reported here was taken after 5–10 min from the time the compound was added to the buffer solution. The absorptions at λ_{max} 303 and 243 mμ did not change during this interval.

Anal. Calcd for $C_8H_9NO_4 \cdot HCl$: C, 43.75; H, 4.59; N, 6.38. Found: C, 43.84; H, 4.73; N, 6.42.

4′,5′-(Dimethoxyoxime)-3-hydroxy-2-methylpyridine (*o*-Pyridoxidial Dimethoxyoxime) (XI).—To a solution of 204 mg (2.4 mmol) of methoxyamine hydrochloride in 20 ml of distilled water 220 mg (1 mmol) of *o*-pyridoxidial hydrochloride (X), dissolved in 10 ml of distilled water, was added drop by drop with stirring. After the addition was complete, 500 mg of sodium acetate dissolved in 10 ml of distilled water was added to bring the reaction mixture to pH 5–6. The mixture was cooled in a refrigerator and the precipitated oxime was filtered and recrystallized from an ethanol–water mixture to yield 198 mg (88.5%) of white, needle-shaped crystals of dimethoxyoxime (XI): mp 106–107°; $\lambda_{max}^{0.1\ N\ HCl}$ 331 mμ (sh) (ε 8.5 × 10³), 311 (11.3 × 10³), 305 (sh) (11.0 × 10³), and 243 (16.8 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 362 mμ (ε 7.8 × 10³) and 236 (20.2 × 10³).

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 54.04; H, 5.37; N, 19.16.

4′,5′-Bisthiosemicarbazone-3-hydroxy-2-methylpyridine (*o*-Pyridoxidial Bisthiosemicarbazone) (XII).—A solution of 220 mg of *o*-pyridoxidial hydrochloride (X) in 5 ml of distilled water was added drop by drop with stirring to the warm solution of 250 mg of thiosemicarbazide in 10 ml of distilled water. After adding 170 mg of sodium acetate, the reaction mixture was allowed to cool, whereupon 200 mg (64.3%) of crude bisthiosemicarbazone precipitated out. A portion was recrystallized from 95% ethanol and dried over phosphorous pentoxide at 80° under high vacuum when an orange red compound, mp 172–174° dec, was obtained.

Anal. Calcd for $C_{10}H_{13}N_7OS_2 \cdot H_2O$: C, 36.46; H, 4.59; N, 29.76; S, 19.46. Found: C, 37.26; H, 4.33; N, 30.16; S, 19.89.

1,3-Dihydro-1,3-dimethoxy-6-methyl furo[3,4-*c*]pyridin-7-ol[39] (*o*-Pyridoxidial Dimethyl Acetal) (XIII).—*o*-Pyridoxidial hydrochloride (X) (0.5 g) dissolved in 50 ml of anhydrous methanol[33] was heated with protection from moisture in an oil bath and kept at 50–60° for 5 days. The reaction mixture was cooled, ammonia gas was bubbled into it, and then it was concentrated to a very small volume. Excess of ether was added and the mixture was filtered. The filtrate was evaporated to dryness, the residue was extracted with chloroform, the extract was concentrated to about 50 ml, and excess of petroleum ether was added to it. The mixture was kept in a refrigerator overnight, yielding the dimethyl acetal XIII. It was recrystallized four times with chloroform–petroleum ether mixture to yield 0.215 g (44.8%): mp 164–165°; $\lambda_{max}^{0.1\ N\ HCl}$ 288 mμ (ε 9.3 × 10³) and 227 (3.8 × 10³); $\lambda_{max}^{0.1\ N\ NaOH}$ 304 mμ (ε 8.1 × 10³) and 241 (9.7 × 10³).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 57.13; H, 6.25; N, 6.61.

Sodium Borohydride Reduction of 4,5-Diformyl-3-hydroxy-2-methylpyridine Hydrochloride (*o*-Pyridoxidial Hydrochloride) (X).—Over a period of 15 min, a solution of 100 mg of *o*-pyridoxidial hydrochloride (X) in 5 ml of 90% methanol was added drop by drop with stirring to a solution of 50 mg of sodium borohydride in 5 ml of 0.1 *N* methanolic sodium hydroxide. In another 15 min of stirring the reaction was complete. The excess of sodium borohydride was decomposed with a few drops of concentrated hydrochloric acid. The solution was evaporated to dryness under reduced pressure; the solid residue extracted twice with 5-ml portions of absolute ethanol and filtered. To the filtrate excess of anhydrous acetone was added and the mixture was kept overnight in a refrigerator yielding 80 mg (85%) of needle-shaped crystals. This compound was identified as pyridoxol hydrochloride (XIV), based upon its melting point and mixture melting point of 208–209° with an authentic sample and its ultraviolet and infrared spectra which were found to be identical with those of the authentic sample. Pyridoxol was also obtained when pyridoxal and isopyridoxal were treated with sodium borohydride under the conditions described above.

Registry No.—III, 15833-01-9; V, 15833-02-0; VI, 15833-03-1; VII, 15833-04-2; VIII, 15833-05-3; IX, 15832-16-3; X, 15832-17-4; XI, 15832-18-5; XII, 15832-19-6; XIII, 15832-20-9.

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N-Vinyl Derivatives of Substituted Pyrimidines and Purines[1]

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The preparation of potentially polymerizable compounds containing heterocyclic moieties of nucleic acids is described. 1-Vinyluracil was prepared by dehydrochlorination of 1-(2-chloroethyl)uracil (**3**). 1-Vinyl-3-methyluracil, 1-vinyl-4-ethoxy-2-pyrimidinone (**7**), 6-chloro-9-vinylpurine (**8**), and 2,6-dichloro-9-vinylpurine (**9**) were prepared from the unsubstituted heterocycles by a vinyl interchange reaction with vinyl acetate, catalyzed by mercuric acetate and sulfuric acid.

The importance of nucleic acids has resulted in many studies on their intramolecular forces using model systems.[2,3] Among possible model systems are polymers containing the heterocyclic moieties of nucleic acids but differing from them in the connecting backbone. To date only a few papers have been published on such models. The necessary macromolecules were usually prepared by attaching heterocycles to cellulose derivatives.[4–9] Only recently Cassidy and Jones[10] described the preparation and properties of polymers based on 5′-O-acrylthymidine. In our laboratory, a program has been started in this direction. The present paper describes the preparation of the N-vinyl derivatives of substituted pyrimidine and purine heterocycles with substituents suitable for subsequent conversion into heterocycles of nucleic acids (uracil, cytosine, adenine and guanine). This approach avoids possible difficulties with functional groups (*e.g.*, the amino group) during the polymerization reaction. N-Vinyl polymers were chosen since they have been well studied and because related poly-

(1) Supported in part by Program Project Grant, National Institutes of Health (GM 10802-04), and by a grant from the National Science Foundation (GB 5483).

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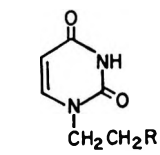
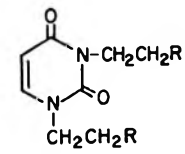
mers of N-vinylpyrrolidinone and N-vinyl-2-oxazolidinone are reasonably soluble in water.[11,12] As the intended physicochemical and biological studies on these compounds may require relatively large amounts of material, different routes to the desired products were tested.

For the uracil series the simplest monomer is 1-vinyluracil. Two approaches for synthesis of this compound were adopted. The first approach is by means of an appropriate elimination reaction, starting from the known[13,14] 1-(2-hydroxyethyl)-uracil. This compound (1) was prepared by Prystas and Gut[13] by treating uracil with ethylene carbonate and subsequent separation from the accompanying disubstituted derivative (2) by chromatography. We modified the reaction for large-scale preparation and tested other approaches for the separation of the mixture. Recrystallization does not give good results and the separation through salt formation procedure is not practical, as the compound 2 is rather hydrophilic. Eventually we found that by addition of excess reagent it is possible to convert the mixture nearly quantitatively into the corresponding chlorides **3** and **4** or the acetates **5** and **6**, and, as the properties of these derivatives are very different, the separation by crystallization is easy. For the preparation of 1-vinyluracil, the most practical procedure was found to be the dehydrochlorination of **3** with potassium *t*-butoxide in dimethyl sulfoxide at room temperature.[15] Other dehydrochlorination procedures for **3**, such as reaction with potassium *t*-butoxide in boiling *t*-butyl alcohol[16] or reaction with alkalies under conditions successfully used for preparation[17] of N-vinyl pyrrolidinone, gave very low yields. Pyrolysis of acetate **5**, a procedure which requires the temperature to be above 600°, also produced only a small amount of 1-vinyluracil with most of the starting material unchanged. We also tested acidic dehydration of **1** at 180° but the yield of the vinyl compound is very low. Another synthetic approach is the vinyl interchange reaction with vinyl acetate catalyzed by mercuric acetate and sulfuric acid;[18] such a reaction was successful with a few heterocycles.[19] An attempt was made first on the vinylation of 3-substituted derivatives of uracil, such as 3-methyluracil. The latter compound was prepared by a new route—methylation of 1-acetyluracil with diazomethane and subsequent hydrolysis. The vinylation procedure gave 1-vinyl-3-methyluracil which was identical with the substance prepared by diazomethane from 1-vinyluracil; the structure **1** previously proposed on the basis of spectral data[13] is thus confirmed by a chemical method. However, the vinylation reactions on 3-benzoyluracil and uracil were not successful.

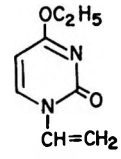
For the cytosine series the simplest monomer would be 1-vinylcytosine with the amino group blocked. Attempts to prepare such a compound by vinylation



1, R=OH
3, R=Cl
5, R=OCOCH$_3$



2, R=OH
4, R=Cl
6, R=OCOCH$_3$



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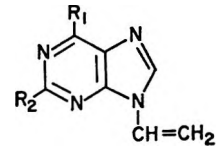

8, R$_1$=Cl , R$_2$=H
9, R$_1$=R$_2$=Cl

of N-acetylcytosine or cytosine were unsuccessful. Fortunately, vinylation was found to be applicable to 4-ethoxy-2-pyrimidinone.[20] The starting compound can exist in two tautomeric forms—1H and 3H; similarly there are two possible N-vinyl derivatives. However, only one product was isolated. Hydrogenation and hydrolysis of this product gave 1-ethyl-5,6-dihydrouracil; the structure therefore must be as given by formula **7**; the N-vinyl derivative of the predominant tautomeric form.[21,22] The polymer prepared from vinyl compound **7** can be the starting material for both the uracil and cytosine series; both amination and hydrolysis of a 4-ethoxy group has been previously demonstrated for the 4-ethoxy-2-pyrimidinone[20] and its N-1-ribosyl derivative.[23]

For the purine series, chlorine-substituted heterocycles were chosen as starting materials. The reason for this choice is that 6-chloro-9-ethylpurine can be converted into 9-substituted derivatives of adenine or hypoxanthine;[24] and the 2,6-dichloro derivatives probably can be converted into guanine derivatives due to the large difference in reactivity of these two chlorine atoms.[25,26] Vinylation of 6-chloro- and 2,6-dichloropurine gave good yields of vinyl derivatives. Again there are two possibilities for the vinyl substitution, namely, at positions 7 or 9. Since the addition of similarly substituted purines to dihydropyran has been found to furnish mainly the 9-substituted derivatives,[27] it appears likely that the vinylation reaction, which starts probably by an addition of the heterocycle or its mercury derivatives to the vinyl double bond,[28,29] would also yield 9-substituted compounds. This hypothesis was confirmed by hydrogenation of the isolated vinyl derivatives **8** and **9**. Both compounds yielded 9-ethylpurine as the reaction product which proves that the designated structures for the vinyl derivatives **8** and **9** are correct.

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The study of polymerization reactions of all five vinyl derivatives is presently underway in our laboratory.

Experimental Section

Melting points were determined on the hot stage and are corrected. Purity of compounds was checked by chromatography, using either a descending system on Whatman No. 40 paper or an ascending system on silica gel, Eastman Sheet 6060.

The compounds were located by their absorption of ultraviolet light.

Water saturated 1-butanol was used as eluent for all the chromatographic systems including the column chromatography described in later sections.

Ultraviolet spectra were measured in a Cary 15 spectrophotometer. Spectra were taken within 12 min from the time of addition of the compound to the solvent, and then repeated three times at 5-min intervals to ensure that no change occurs owing to decomposition during measurement. Pyrimidines were dissolved in phosphate buffer (0.05 *M* in phosphate, pH 7) and purines were dissolved in 95% ethanol since the amount of purines dissolved in aqueous buffer within a 12-min period was usually too low for the measurement.

Microanalyses were by Spang Microanalytical Laboratory, Inc., Ann Arbor, Mich., and Galbraith Laboratories, Inc., Knoxville, Tenn.

1-(2-Hydroxyethyl)uracil (1) and 1,3-Di(2-hydroxyethyl)uracil (2).—Uracil (89.6 g) and its monosodium salt (2 g) were dissolved in dry, hot dimethylformamide (1300 ml). To the boiling stirred solution, ethylene carbonate (72 g) in dimethylformamide (150 ml) was added dropwise. After boiling for 1 hr the solution was evaporated *in vacuo* (60°). Ethanol was added and the mixture was repeatedly evaporated *in vacuo* to remove the remaining dimethylformamide. The residue was dissolved in hot water (700 ml). The addition of Dowex 50 W (H^+ form) brought the solution to pH 5. After filtration, the solvent was removed *in vacuo* and the residue extracted with 1 l. of boiling ethanol; most of the uracil remained undissolved. The mixture was filtered; evaporation of the filtrate gave white crystals of **1** and **2** and a small quantity of uracil. A crystalline mixture of **1** and **2** (85 g) was obtained following extraction with ethyl acetate in a Soxhlet apparatus. This mixture was separated by column chromatography on cellulose; Prystas and Gut[13] used a 1:150 ratio of substance–cellulose; we found that it can be reduced to 1:50. The melting points of separated **1** (138°) and **2** (154°) corresponded to the published values.[13,14]

1-(2-Chloroethyl)uracil (3).—Pyridine (0.5 ml) was added to a solution of a mixture of **1** and **2** (16 g) in dry, hot dioxane (350 ml). Thionylchloride (30 ml) in dioxane (20 ml) was added dropwise and the solution was boiled for 1 hr. The solvent was then evaporated *in vacuo* and the residue was dissolved in 800 ml of chloroform. The chloroform solution was filtered and the filtrate extracted three times by 50 ml of water. The organic phase was dried (magnesium sulfate), filtered, and evaporated and the residue dissolved in hot dioxane. After cooling, *ca.* 6 g of crystals was collected and recrystallized from dioxane, mp 164–167° (identical with the melting point of the substance reported by Prystas and Gut[13]). The water extracts contained a mixture of **1** and **3** which can be recycled. It is interesting to note the difference in reactivity between **1** and uracil-1-acetic acid with respect to thionyl chloride. The former reacts at room temperature, whereas attempts of our own and others[30] to convert the acid into the chloride were unsuccessful.

1,3-Di(2-chloroethyl)uracil (4).—The dioxane mother liquors obtained from the crystallization of **3** were evaporated. The residue was dissolved in chloroform, extracted first by 1 *N* sodium hydroxide and then by water, and dried (magnesium sulfate). A colorless oil was obtained after evaporation which distilled at a bath temperature of 160° (0.07 mm). The identical substance was prepared from the pure diol **2** by thionylchloride.

Anal. Calcd for $C_8H_{10}N_2O_2Cl_2$: C, 40.53; H, 4.25; N, 11.82. Found: C, 40.31; H, 4.24; N, 12.05.

1-(2-Chloroethyl)-3-methyluracil.—This compound was prepared from **3** by reaction with excess diazomethane in ether–dioxane solution for 5 days at room temperature. It was recrystallized from water, mp 88–89°.

Anal. Calcd for $C_7H_9N_2O_2Cl$: C, 44.57; H, 4.81; N, 14.85. Found: C, 44.63; H, 4.94; N, 14.95.

1-(2-Acetoxyethyl)uracil (5).—A suspension of **1** and **2** (obtained from Soxhlet extraction, 10 g) was stirred overnight in acetic anhydride (200 ml) and pyridine (0.1 ml). Methanol was added to the clear solution, which was evaporated *in vacuo*. The residue was dissolved in hot ethyl acetate and cooled; white crystals (5 g) of **5** were obtained. These were recrystallized from ethyl acetate and ethanol, mp 136–138°. The identical substance was prepared by similar acetylation of the pure alcohol **1**.

Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.43; H, 5.07; N, 14.14.

1,3-Di(2-acetoxyethyl)uracil (6).—The ethyl acetate mother liquor obtained from the crystallization of **5** was evaporated. The residue was treated by an identical procedure described for the preparation of compound **4**. After the evaporation of the dried chloroform, a yellow oil which slowly crystallized was obtained: bp 180° (bath) (0.07 mm); mp 50–52°. The identical substance was prepared by acetylation of the pure diol **2**.

Anal. Calcd for $C_{12}H_{16}N_2O_6$: C, 50.70; H, 5.67. Found: C, 51.23; H, 5.97.

1-(2-Acetoxyethyl)-3-methyluracil.—This compound was prepared from **5** by reaction with diazomethane in ether–dioxane solution for 5 days. A colorless oil, distilled at a bath temperature of 160° (0.07 mm), was obtained.

Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70. Found: C, 50.81; H, 5.86.

1-Vinyluracil.—The chloride **3** (2.5 g) was dissolved in dry dimethyl sulfoxide (20 ml) and added dropwise to the stirred solution of 5.1 g of potassium *t*-butoxide in 20 ml of dimethyl sulfoxide. After an hour at room temperature, 60 ml of cold water was added and the solution was made slightly acidic by adding Dowex 50 W (H^+ form). The filtered solution was evaporated *in vacuo* (0.1 mm) under 60°. A crop of crystals was obtained which was recrystallized from ethanol. This procedure gave 1.2 g of 1-vinyluracil (yield 60%) contaminated by alcohol **1**. The pure compound was prepared by chromatography on cellulose (50 g). The vinyl compound (eluted before the alcohol) sublimed *in vacuo:* mp 188–189°; λ_{max} (buffer, pH 7) 277 mμ (ε 10,800) and 223 mμ (ε 10,400); λ_{min} 245 mμ; λ_{max} (0.01 *N* sodium hydroxide) 277 mμ (ε 10,100) and 222 mμ (ε 11,600); λ_{min} 252 mμ, shoulder 232 mμ.

Anal. Calcd for $C_6H_6N_2O_2$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.05; H, 4.37; N, 20.38.

1-Vinyl-3-methyluracil.—1-Vinyluracil (35 mg) was dissolved in methanol (3 ml) and excess diazomethane in ether was added. After 24 hr the solution was evaporated and the residue was chromatographed on a 2-mm layer of silica gel. The main ultraviolet light absorbing zone was eluted. Crystals were obtained after evaporation and were sublimed *in vacuo:* mp 92–94°; infrared spectrum identical with that of the 1-vinyl-3-methyluracil prepared by the vinylation reaction.

Pyrolysis of Acetate 5.—A vycor glass tube, sealed at one end, was loaded with 1.4 g of acetate **5**, 30 mg of hydroquinone, and Vycor glass fillings (20-cm zone). The part with glass fillings was placed into furnace maintained at 620°; the tube was evacuated to 10 mm; and acetate **5** was distilled slowly throughout the heated zone. A brown distillate was collected, treated with charcoal in ethanol, and fractionally recrystallized from ethanol. Considerable amount of starting acetate (600 mg) was recovered; the other fractions gave, by chromatography on cellulose, 0.1 g (10%) of 1-vinyluracil, which was identical with the substance prepared from the dehydrochlorination experiment.

3-Methyluracil.—1-Acetyluracil was prepared by the method of Spector and Keller[31] from uracil and acetic anhydride. This compound (13 g) was dissolved in 200 ml of hot dioxane. Then, using a Dry Ice condenser, an ethereal solution of diazomethane was added in excess. After 1 day the mixture was evaporated, the residue was dissolved in 45 ml of ethanol, and 45 ml of 0.25 *M* HCl, and the solution boiled for 1 hr. According to chromatography, both uracil and 3-methyluracil were present; the mixture was separated by fractional sublimation (140°, 0.05 mm) to give 3-methyluracil as the sublimate (8 g, 75% yield), mp 179–183°, identical with the sample prepared by a known route.[32]

(30) B. R. Baker and G. B. Chheda, *J. Pharm. Sci.*, **54**, 25 (1965).

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3-Benzoyluracil was prepared by hydrolysis of 1,3-dibenzoyluracil.[33] In our hands it had mp 216° dec instead of 198–201° reported previously.[33]

As the melting point (151–152°) of the reaction product of our compound with diazomethane is the same as that of the 1-methyl-3-benzoyluracil,[33] this difference in the reported melting point may be due to a difference in the rate of heating.

Vinylation Reaction. General Procedure.—A solution of 0.1 ml of concentrated sulfuric acid in ethyl acetate (2 ml) was added to a suspension of 0.5 g of mercuric acetate in 100 ml of vinyl acetate in a pressure flask; a clear solution was formed. This procedure avoids the coloring of vinyl acetate by the direct addition of acid. Then the powdered heterocyclic compound (about 2 g) was added followed by another 50 ml of vinyl acetate. After bubbling with nitrogen for 10 min the flask was closed and placed in a bath at 45–50° with occasional agitation for 1–5 days. After the specified period, dry sodium acetate was added, and the mixture stirred for 10 min and then filtered. The filtrate was evaporated *in vacuo* and the residue was dissolved in chloroform. The solution was then extracted with cold 1 *N* sodium hydroxide; occasionally centrifugation was necessary to facilitate the removal of the aqueous layer. The chloroform layer was dried (magnesium sulfate) and evaporated. The residue was purified by recrystallization and sublimation *in vacuo*. Yields of the vinyl compounds varied; the governing factors[28] appear to be the rate of the solution of the starting material which is difficult to control and the rate of the competing decomposition. All procedures reported below have been repeated successfully several times.

A. **3-Methyluracil.**—The reaction time was 6 days. 1-Vinyl-3-methyluracil was recrystallized from cyclohexane: mp 95–97°; λ_{max} (buffer pH 7) 276 mμ (ε 10,500) and 221 mμ (ε 10,500); λ_{min} 246 mμ. In another experiment the reaction time was 10 days; the main portion of the product was polymerized.

Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.04; H, 5.51; N, 18.04.

B. **3-Benzoyluracil** was sparingly soluble in the vinylation solution and the reaction gave brown products of polymerization and decomposition.

C. **Uracil, cytosine, and N-acetylcytosine** in the vinylation reaction gave small quantities of oily materials which were not homogeneous; infrared and ultraviolet spectra indicated that only minute quantities of vinylsubstituted heterocycles were present.

D. **4-Ethoxy-2-pyrimidinone** was prepared according to Hilbert and Jansen;[20] the purity was checked by paper chromatography using described elution systems.[21,22] Vinylation (2 days) of 1.1 g gave 0.7 g (55%) N-1 vinyl derivative **7**: white crystals (cyclohexane); mp 77–78°; λ_{max} (buffer pH 7) 287 mμ (ε 8600) and 211 mμ (ε 13,600); λ_{min} 251 mμ.

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.96; H, 5.95; N, 16.99.

E. **6-Chloropurine.**—Vinylation (5 days) of 2 g of the starting compound gave 1.6 g (70%) of 6-chloro-9-vinylpurine **8** that was recrystallized from ethanol: mp 166–167°; λ_{max} (95% ethanol) 263 mμ (ε 7500) and 224 (ε 25,700); λ_{min} 249 mμ.

Anal. Calcd for $C_7H_5N_4Cl$: C, 46.55; H, 2.79; N, 31.02. Found: C, 46.55; H, 2.70; N, 31.36.

F. **2,6-Dichloropurine.**—Reaction time was 2 days; 1.4 g (80%) of crystalline vinyl compound **9** was obtained from 1.5 g of starting material. This was recrystallized from ethanol: mp 126–127°; λ_{max} (95% ethanol) 274 mμ (ε 7800) and 228 mμ (ε 27,600); λ_{min} 252 mμ, shoulder at 235 mμ.

Anal. Calcd for $C_7H_4N_4Cl_2$: C, 39.09; H, 1.87; N, 26.05. Found: C, 39.58; H, 1.49; N, 25.89.

Hydrogenation of 6-Chloro-9-vinylpurine (8) and of 2,6-Dichloro-9-vinylpurine (9).—Magnesium oxide (45 mg) and palladium on charcoal (5%, 45 mg) were added to a 20-ml solution of ethanol–water (v/v 1:1) containing 90 mg of the chloro derivative. The solution was hydrogenated at room temperature and atmospheric pressure; the consumption of hydrogen practically stopped after 1 hr when the theoretical amount was consumed. The mixture was filtered and 150 mg of potassium carbonate was added to the filtrate which was then evaporated. The residue was extracted with carbon tetrachloride and the resulting extract was dried (magnesium sulfate).

Crystalline 9-ethylpurine was obtained after evaporation of the extract; it gave an infrared spectrum identical with that of the authentic sample.[34] In preliminary experiments, acetone was used for extraction; crystallization was very slow.

Hydrogenation and Hydrolysis of 1-Vinyl-4-ethoxy-2-pyrimidinone (7).—Hydrogenation was conducted as described immediately above with 90 mg of vinyl compound in 20 ml of ethanol–water solution (1:1 v/v) containing 45 mg of palladium on charcoal (5%). The filtered solution was evaporated *in vacuo;* the residue was dissolved in 20 ml of hydrochloric acid (1 *N*), left overnight, and again evaporated. After sublimation *in vacuo*, the infrared spectrum of the sublimate was identical with the spectrum of 1-ethyl-5,6-dihydrouracil. The compound for comparison was purchased from Cyclo Chemical Corp., Los Angeles, Calif., and was purified by vacuum sublimation.

The product of hydrogenation and hydrolysis was shown by paper chromatography to contain a very small amount of 1-ethyluracil, undetected in the infrared spectrum.

Registry No.—**1**, 936-70-9; **2**, 711-66-0; **3**, 15816-10-1; **4**, 15816-11-2; **5**, 15765-13-6; **6**, 15765-14-7; **7**, 15765-15-8; **8**, 15816-12-3; **9**, 15816-13-4; 1-(2-chloroethyl)-3-methyluracil, 15816-14-5; 1-(2-acetoxyethyl)-3-methyluracil, 15765-16-9; 1-vinyluracil, 15765-17-0; 1-vinyl-3-methyluracil, 15765-18-1.

Acknowledgment.—We gratefully thank Dr. Cecil H. Robinson and colleagues in our laboratory for helpful comments and discussion.

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(34) We are indebted to Dr. J. A. Montgomery for this sample.[24]

A New Synthesis and Alkylations of Some Pyrimido[1,2-a]indoles

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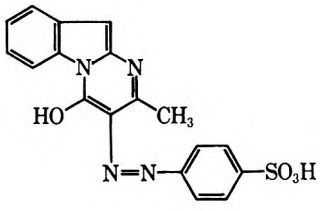
A new synthesis of pyrimido[1,2-a]indoles has been developed utilizing a base-catalyzed cyclization of a 2-(cyanomethyl)anilinomethylenemalonate. The mode of formation of this ring system and its structure proof are discussed. Base-catalyzed alkylations of pyrimido[1,2-a]indoles give mixtures of 1- and 10-substituted products 6 and 7a, respectively. Hydrogenation or metal hydrides cause the reduction of the double bond. Decomposition occurs during attempted acid or base hydrolyses of these molecules.

In connection with studies in these laboratories on the reactions of derivatives of arylaminomethylenemalonates,[1] compound **1** was treated with 1 equiv of sodium ethoxide in refluxing ethanol. The product obtained, a stable orange solid, was shown to be the salt **2** which on acidification, gave the pyrimido[1,2-a]-indole derivative **3** in 84% over-all yield. This product was probably formed by the mechanism in Scheme I.

The structure of **3** was established by microanalyses and infrared and nmr spectra (see Experimental Section). The lactam rather than the tautomeric hydroxy imine structure was deduced from the infrared spectrum which showed a strong band at 1660 cm^{-1}, whereas the alternative structure should not exhibit a band above 1600 cm^{-1}.[2]

Only two examples of syntheses of pyrimido[1,2-a]indoles could be found in the literature. One[3] involves the reaction of ethyl 4-sulfobenzeneazoacetoacetate with 2-aminoindole to give **4** in 75% yield,



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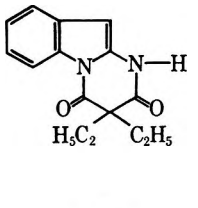

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while the other[4] describes the isolation of the dilactam **5** in 20% yield, as a by-product, from the reaction of 2-aminoindole and diethylmalonyl dichloride.

Since a facile synthesis of pyrimido[1,2-a]indoles was now available to us, a number of reactions, particularly alkylations, of these systems were investigated.

Hydrogenation of **3** over platinum (see Scheme II) gave the corresponding dihydro compound **10**. This transformation was also achieved with sodium borohydride. Lithium aluminum hydride failed to reduce **3** in ether, although the same reagent in refluxing tetrahydrofuran gave a complex mixture which was not studied.

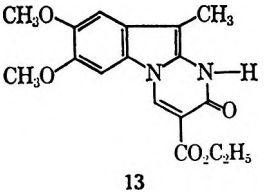
Alkylation of the salt **2** with methyl iodide or ethyl bromoacetate in a variety of solvents (ethanol, water, dimethylformamide, benzene) led in all cases to mixtures. The isomeric products arising from the ethyl bromoacetate reaction in ethanol were shown to be **6** and **7a** (Scheme II). The position of alkylation in **6** was established by examination of the nmr spectrum of its hydrogenation product (**8**) (**6** was not sufficiently soluble in suitable solvents) which did not show a peak between 5.5 and 6.0 ppm characteristic of the hydrogen in the 10 position in **3** and other compounds in this series. Compound **7a** exhibited a singlet for one proton at 5.64 ppm, indicating that alkylation had occurred on either the nitrogen or the oxygen of the lactam. The "C" ring in both **7a** and its hydrogenation product **9** were stable to dilute, refluxing hydrochloric acid.

The ultraviolet spectra of **7a** in neutral and acidic media were identical. The same holds true for **9**. The infrared spectrum of **7a** exhibited a strong band at 1664 cm^{-1}, while **9** had a band at 1680 cm^{-1}. On the basis of this evidence, structure **7a** rather than its O-alkylated analog, is proposed.

Whereas cyanoethylation of **2** or **3** failed to give a product (starting material was recovered in both cases), compound **10** was dicyanoethylated with acrylonitrile and triethylamine. The presence of the C–H in the 10 position in the nmr spectrum indicated that cyanoethylation had not taken place on this carbon; instead, cyanoethylation had occurred to the carbethoxy group and either on nitrogen or oxygen. A band at 1680 cm^{-1} in the ir spectrum suggested that the lactam carbonyl was unchanged; hence structure **11a** is indicated for the cyanoethylation product.

The unsubstituted lactams **3** and **10** were unstable to both aqueous acid and base,[5] whereas their N-substituted derivatives **7a** and **11a** were stable to these reagents. In fact, **7a** was hydrolyzed smoothly to **7b** in dilute hydrochloric acid and treatment of **11a** with aqueous sodium hydroxide gave the decarbethoxylated dinitrile **12**.[6]

The sequence of reactions (**1** to **3**) was carried out with the α-methylacetonitrile analog of **1**, to give **13** as the final product. Therefore, it appears that 10-substituted pyrimido[1,2-a]indoles of the type **13** may also be prepared by this method.



13

(1) W. F. Gannon and E. A. Steck, *J. Org. Chem.*, **27**, 4137 (1962).

(2) 4-Pyrimidone shows bands in the region 1600–1700 cm^{-1}, while 4-methoxypyrimidine does not [see D. J. Brown and L. N. Short, *J. Chem. Soc.*, 331 (1953)].

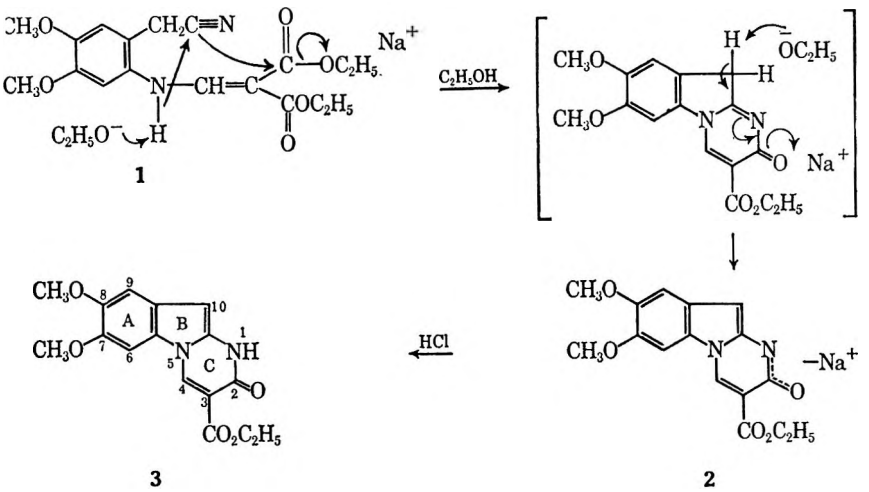
(3) U. S. Patent 2,432,419 (Dec 9, 1947); *Chem. Abstr.*, **42**, 2194a (1948).

(4) A. Ebnöther, *et al.*, *Helv. Chim. Acta*, **42**, 918 (1959).

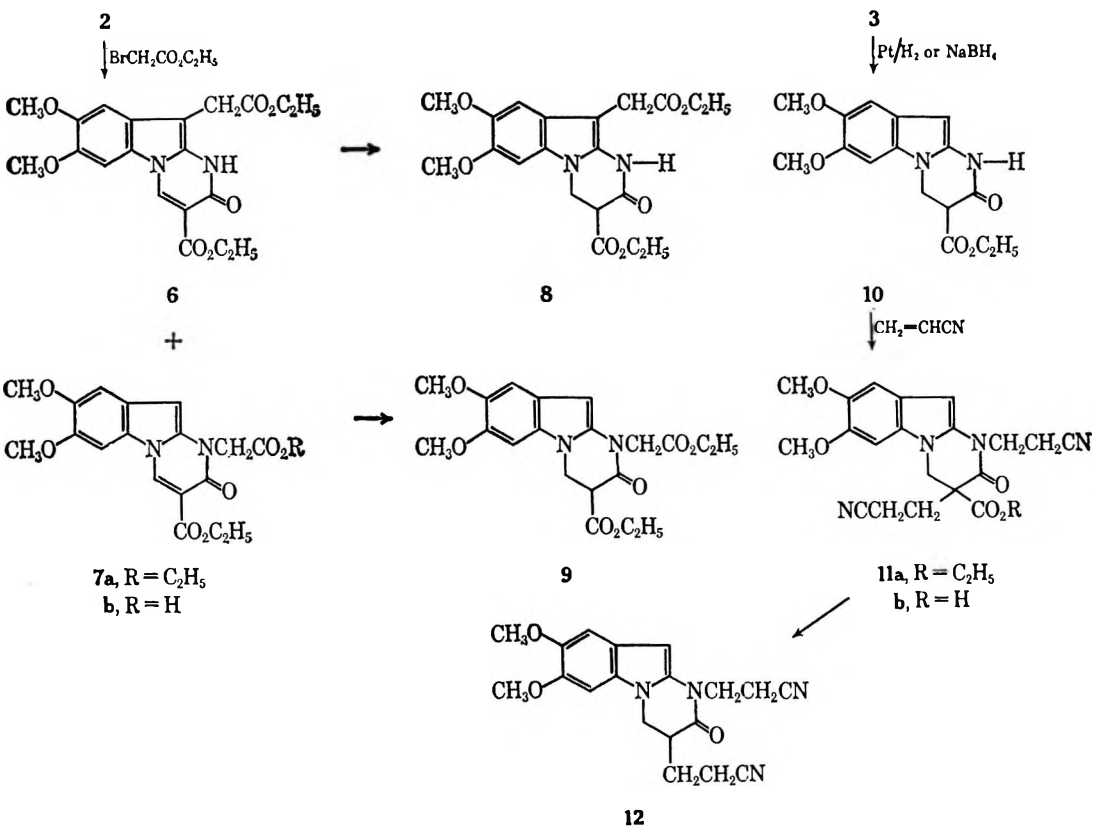
(5) Solutions of these lactams in aqueous ethanolic acid or base darken rapidly and only small amounts of water-insoluble, tarry materials are recovered. The lactam function presumably is hydrolyzed, leading to an amino indan which is quite susceptible to air oxidation.

(6) This product might arise from saponification of the ester followed by decarboxylation of the resulting α-amido acid (**11b**) or alternatively from hydrolysis of the lactam followed by decarboxylation of the resulting α-carbethoxy acid and cyclization back to the lactam.

SCHEME I



SCHEME II



In general, the comparable order of reactivity of the many functional groups present in these systems and the hydrolytic instability of the unsubstituted lactam group limited the synthetic versatility of these molecules.

Experimental Section

All melting points are corrected and were taken in a stirred, oil bath. Infrared spectra were obtained on Perkin-Elmer Model 21 spectrometer and ultraviolet spectra on a Cary Model 14 spectrometer. The nmr spectra were determined on a Varian A-60 spectrometer at room temperature. The solutions were approximately 20% (w/v). Tetramethylsilane was used as an internal standard.

Diethyl [(2-Cyanomethyl-4,5-dimethoxy)anilino]methylenemalonate (1).—(2-Amino-4,5-dimethoxyphenyl)acetonitrile[7] (13.1 g, 0.068 mol) was refluxed with diethyl ethoxymethylenemalonate (14.8 g, 0.068 mol) in 170 ml of benzene for 2 hr. Concentration of the solvent to one-third its original volume separated a solid which was collected by filtration and recrystallized from benzene to give 20.0 g (80%) of diethyl [(2-cyanomethyl-4,5-dimethoxy)anilino]methylenemalonate as off-white crystals: mp 152–153°; $\nu_{max}^{CHCl_3}$ 2250 (C≡N), 1692 (C=O vinylogous carbamate), and 1610 cm^{-1} (C=C); $\lambda_{max}^{CH_3OH}$ sh 221 mμ (ε 17,900) and 320 mμ (ε 18,600).

Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.28; H, 6.10; N, 7.79.

3-Carbethoxy-7,8-dimethoxypyrimido[1,2-*a*]indol-2(1H)-one (3).—To a solution of sodium ethoxide, prepared from 3.2 g

(7) G. N. Walker, *J. Am. Chem. Soc.*, **77**, 3844 (1955).

(0.14 g-atom) of sodium and 300 ml of ethanol was added 50 g (0.14 mol) of diethyl [(2-cyanomethyl-4,5-dimethoxy)anilino]-methylenemalonate as a slurry in 500 ml of ethanol, and the resulting mixture was refluxed for 3 hr. The separated orange solid (the sodium salt 2) was collected by filtration, washed with ethanol, and dried. It was then dissolved in water and the solution was made acidic (pH 5) with 10% hydrochloric acid. Upon standing at 4° for 18 hr the solution deposited a yellow solid and was filtered to give 36.5 g (84%) of 3-carbethoxy-7,8-dimethoxypyrimido[1,2-a]indol-2(1H)-one, mp 239–241°. Two recrystallizations from dimethylformamide afforded yellow flakes: mp 240–241°; ν_{max}^{Nujol} 1695 (C=O conjugated ester) and 1660 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ 278 mμ (ε 29,400), 299 (32,700), and 337 (10,400). The nmr spectrum (DMF-d_7) exhibited a triplet (three protons) at δ 1.32 (–C–CH$_3$ of ester), singlets (three protons each) at 3.87 and 3.93 (methoxy), a quartet (two protons) at 4.30 (O–CH$_2$– of ester), a singlet (1 proton) at 5.98 (C–H of indole ring), singlets (one proton each) at 7.09 and 7.92 (aromatic C–H), and a singlet (one proton) at 9.10 (vinyl, adjacent to nitrogen).

Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.96; H, 5.16; N, 8.81.

Ethyl 3-Carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido-[1,2-a]indole-10-acetate (6) and Ethyl 3-Carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-1-acetate (7a).—The sodium salt of 3-carbethoxy-7,8-dimethoxypyrimido-[1,2-a]indol-2(1H)-one (13 g, 0.038 mol) was suspended in 400 ml of absolute ethanol. Ethyl bromoacetate (38 g, 0.23 mol) was added and the mixture was refluxed for 1.5 hr. After cooling, the separated solid was collected and recrystallized three times from ethanol to give 2.0 g (13%) of ethyl 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indol-10-acetate as yellow crystals: mp 256–260°; ν_{max}^{KBr} 1720 (C=O of ester), 1692 (C=O conjugated ester), and 1653 cm^{-1} (C=O of amide); $\lambda_{max}^{CH_3CN}$ 281 mμ (ε 26,300) 303 (31,600), and 338 (10,800).

Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.69; H, 5.51; N, 6.96. Found: C, 59.95; H, 5.48; N, 6.83.

The filtrate of the above reaction mixture was allowed to stand at room temperature for 18 hr. The separated solid was isolated by filtration and recrystallized twice from ethanol to give 5.7 g (37%) of ethyl 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-1-acetate as a fluffy yellow solid: mp 208.5–209°; ν_{max}^{KBr} 1730 (C=O ester), 1695 (C=O conjugated ester), and 1664 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3CN}$ 277 mμ (ε 25,900), 300 (29,800), and 335 (10,400). The nmr spectrum ($CDCl_3$) exhibited appropriate peaks for 2 ethyl, 2 methoxy, and aromatic C–H groups and in addition a singlet (two protons) at δ 4.80 (–CH$_2$– adjacent to ester and nitrogen), a singlet (one proton) at 5.64 (CH of indole), and a singlet (one proton) at 8.50 (vinyl adjacent to nitrogen).

Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.69; H, 5.51; N, 6.96. Found: C, 59.30; H, 5.51; N, 6.75.

3-Carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-indole-1-acetic Acid (7b).—A 21.5-g (0.054 mol) sample of ethyl 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-indole-1-acetate was stirred and refluxed for 1.5 hr in a mixture of 400 ml of 1,2-dimethoxyethane and 400 ml of 10% hydrochloric acid. After cooling, the separated solid was collected and recrystallized from dimethylformamide–water to give 6.6 g (33%) of 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-indole-1-acetic acid as yellow crystals: mp 268–269°; ν_{max}^{KBr} 1735 (broad, C=O for conjugated ester and nonconjugated acid) and 1630 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ 274 mμ (ε 31,200), 296 (27,100), and 332 (9800).

Anal. Calcd for $C_{18}H_{18}N_2O_7$: C, 57.75; H, 4.85; N, 7.48. Found: C, 57.66. H, 4.77; N, 7.51.

Ethyl 1,2,3,4-Tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-indole-3-carboxylate (10). A.—A suspension of 9.5 g (0.03 mol) of 3-carbethoxy-7,8-dimethoxypyrimido[1,2-a]indol-2(1H)-one in 250 ml of ethanol containing 0.9 g of platinum oxide was hydrogenated at room temperature at an initial pressure of 45 psi. The hydrogen uptake stopped after 4 hr, the separated white solid was dissolved by heating and the solution was filtered, the filtrate was diluted to 500 ml with water and cooled. The separated white solid amounted to 6.5 g (68%) of ethyl 1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-3-carboxylate: mp 166–166.5°; ν_{max}^{Nujol} 1730 (C=O ester) and 1680 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ 283 mμ (ε 10,000), 294 (11,800), and 317 (17,800).

Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.56; H, 5.94; N, 8.74.

B.—A 3.16-g (0.01 mol) sample of 3-carbethoxy-7,8-dimethoxypyrimido[1,2-a]indol-2(1H)-one was treated with 1.5 g (0.04 mol) of sodium borohydride in 100 ml of isopropyl alcohol for 5 hr at room temperature. The reaction mixture was poured onto ice containing dilute hydrochloric acid and extracted with chloroform. Removal of the organic solvent left an oil which was crystallized and then recrystallized from aqueous methanol to give a white solid, mp 165–166°, which was in all respects (infrared spectrum, melting points, and a mixture melting point determination) identical with the product obtained in part A above.

Ethyl 1,3-Bis(2-cyanoethyl)-1,2,3,4-tetrahydo-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-3-carboxylate (11a).—A 20-g (0.063 mol) sample of ethyl 1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-3-carboxylate was caused to react with excess (75 ml) acrylonitrile by 24-hr reflux in 300 ml of ethanol containing 10 ml of triethylamine. After concentration of the solvent, the residual oil was chromatographed on neutral alumina (200 g). Fractions eluted with 50% ether–chloroform were combined and concentrated to give a solid which on recrystallization from ethyl acetate–cyclohexane gave 11 g (45%) of ethyl 1,3-bis(2-cyanoethyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-3-carboxylate as white crystals: mp 117–118°; $\nu_{max}^{CHCl_3}$ 2255 (C≡N), 1732 (C=O ester), and 1678 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ 214 mμ (ε 24,400) and 315 mμ (ε 15,400). The nmr spectrum ($CDCl_3$) showed a singlet (one proton) at δ 5.89 (CH of indole) and appropriate peaks for the protons in the rest of the molecule.

Anal. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.48; H, 5.93; N, 13.45.

1,2,3,4-Tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-1,3-dipropionitrile (12).—A 1.15-g (0.0028 mol) sample of ethyl 1,3-bis(2-cyanoethyl)-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-3-carboxylate was saponified by refluxing with 0.12 g of sodium hydroxide in 30 ml of aqueous ethanol for 5 hr. Cooling deposited 1.06 g of a white solid which was suspended in water and acidified with dilute hydrochloric acid. After the gas evolution had stopped, the separated solid was collected and recrystallized from ethanol–dimethylformamide to give 0.67 g (70%) of 1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido-[1,2-a]indole-1,3-dipropionitrile as white crystals: mp 158–159°: ν_{max}^{KBr} 2242 (C≡N) and 1670 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ sh 282 mμ (ε 9500), 291 (11,000), and 315 (17,400).

Anal. Calcd for $C_{19}H_{20}N_4O_3$: N, 15.90. Found: N, 15.87.

3-Carbethoxy-7,8-dimethoxy-10-methylpyrimido[1,2-a]indol-2(1H)-one, (13).—A 77-g (0.35 mol) sample of (2-nitro-4,5-dimethoxyphenyl)acetonitrile[4] was alkylated with 70 g (0.5 mol) of methyl iodide in the presence of 17.5 g (0.35 mol) of sodium hydride, in standard fashion, to give α-(2-nitro-4,5-dimethoxyphenyl)propionitrile (26 g), mp 135–137°. This material, without further characterization, was reduced with palladium on carbon in ethyl acetate[4] to the corresponding amino derivative. The latter was treated with diethyl ethoxymethylenemalonate, as described in the preparation of **5b**. The resulting product, mp 100–105° (3.6 g), was treated with 1 equiv of sodium ethoxide in 150 ml of ethanol as described above (see preparation of **8**). The product, after recrystallization from dimethylformamide, had mp 281–282°; ν_{max}^{KBr} 1730 (C=O ester) and 1685 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ 284 mμ (ε 18,700), 304 (20,600), and 335 (10,000).

Anal. Calcd for $C_{17}H_{18}N_2O_5$: N, 8.48. Found: N, 8.78.

Ethyl 3-Carbethoxy-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-10-acetate (8).—A 2-g sample of ethyl 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-indole-10-acetate was hydrogenated at 50 psi in 120 ml of ethanol in the presence of platinum oxide. After 6 hr the catalyst was filtered and ether was added to the filtrate. The separated solid was recrystallized from dimethylformamide–water to give 1.2 g (60%) of ethyl 3-carbethoxy-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-10-acetate: mp 210.5–211.5°; ν_{max}^{KBr} 1738 (C=O ester) and 1660 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3CN}$ 223 mμ (ε 21,400), sh 282 (10,000), sh 294 (12,400), and 316 (16,300). The nmr spectrum (DMF-d_7) exhibited the usual triplets and quartets for the O–CH$_2$CH$_3$ groups, singlets for the O–CH$_3$ groups, multiplets between 4 and 5 ppm for the protons of the 3 and 4 positions, and two singlets for the aromatic protons.

Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.23; H, 5.83; N, 7.15.

Ethyl 3-Carbethoxy-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]indole-1-acetate (9).—A 10-g sample of ethyl 3-carbethoxy-1,2-dihydro-7,8-dimethoxy-2-oxopyrimido[1,2-a]-

indole-1-acetate was hydrogenated at an initial pressure of 50 psi in 200 ml of ethanol in the presence of 1 g of platinum oxide. After 4 hr the catalyst was filtered, the filtrate was concentrated, and the residual oil was chromatographed on neutral alumina. Fractions eluted with ether were combined and concentrated, and the residual solid was recrystallized from ethyl acetate–hexane to give 3.0 g (30%) of ethyl 3-carbethoxy-1,2,3,4-tetrahydro-7,8-dimethoxy-2-oxopyrimido[1,2-*a*]indole-1-acetate: mp 96–98°; $\nu_{max}^{CHCl_3}$ 1736 (C=O ester) and 1682 cm^{-1} (C=O amide); $\lambda_{max}^{CH_3OH}$ sh 281 mμ (ε 8000), sh 289 (9700), and 314 (15,500).

Anal. Calcd for $C_{20}H_{24}N_2O_7$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.51; H, 5.98; N, 6.84.

Acknowledgment.—We thank Dr. H. R. Almond and Mrs. M. C. Christie for many of the analytical and spectral results.

Synthesis of Some 5-Trimethylsilylindoles

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5-Trimethylsilylindole has been synthesized starting from indole which was N-benzylated and brominated in the 5 position, metalated to 5-lithio-N-benzylindoline, and treated with trimethylchlorosilane to yield 5-trimethylsilyl-N-benzylindoline. Catalytic hydrogenolysis in the presence of acetic anhydride gave 5-trimethylsilyl-N-acetylindoline, which was hydrolyzed by KOH in diethylene glycol to 5-trimethylsilylindoline, which in turn was converted into 5-trimethylsilylindole by catalytic dehydrogenation in boiling xylene in the presence of palladium–charcoal. 5-Trimethylsilylgramines were synthesized. 5-Trimethylsilylgramine methiodide was converted into the nitrile by reaction with sodium cyanide and the latter was hydrolyzed to 5-trimethylsilylindole-3-acetic acid, or reduced to 5-trimethylsilyltryptamine.

Various indole derivatives substituted in the 5 position have been synthesized, such as 5-acetyl-,[1] 5-amino-,[2] 5-chloro-,[3] and 5-fluorotryptamines[4] and 5-nitro- and 5-aminogramines.[5] These are interesting in that they are related to the physiologically active 5-hydroxytryptamine.

We report here the synthesis of 5-trimethylsilylindole and some of its derivatives.

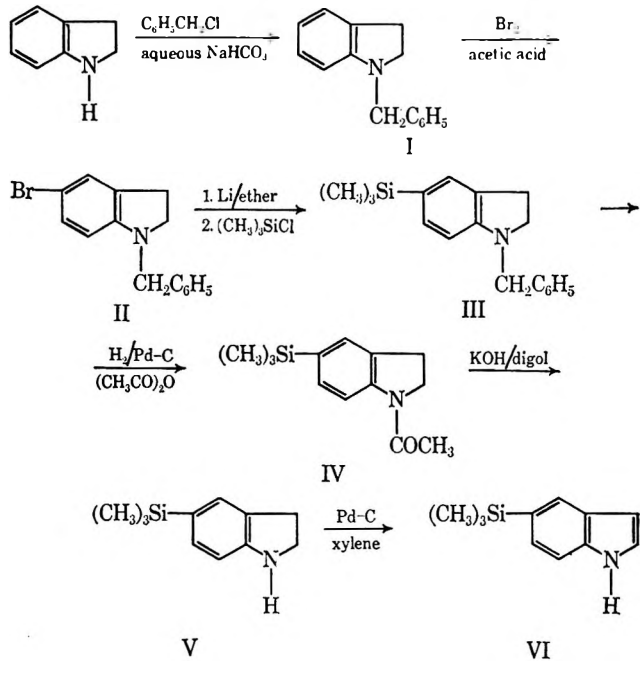
The preparation of compounds having a silicon–aryl bond involves difficulties because of the sensitivity of the silicon–aryl bond, to cleavage by acids and halogens. For this reason, although there are many methods for the preparation of indole derivatives, most of them are unsuitable for the preparation of silicon-containing indole derivatives since they require acid conditions in some step of the synthesis.

5-Trimethylsilylindole was synthesized starting from indoline[6,7] according to Scheme I.

N-Benzylindoline (I) was brominated with 1 equiv of bromine in acetic acid solution giving 5-bromo-N-benzylindoline (II), which was identical (melting point, mixture melting point, and ir spectrum) with the compound resulting from the N-benzylation of 5-bromoindoline.[8]

Catalytic hydrogenolysis of the N-benzyl group from 5-trimethylsilyl-N-benzylindoline (III) was easy, but in methanol, 2-propanol, or acetic acid solution it was accompanied by cleavage of the trimethylsilyl group. This was attributed to activation by the electron-releasing amino group in the *para* position. Consequently,

SCHEME I



hydrogenolysis was done in acetic anhydride, so that after the N-benzyl was split off the amino group was acetylated. The silicon–aryl bond was then stable and the resultant 5-trimethylsilyl-N-acetylindoline (IV) partially precipitated out of solution. The reaction was stopped immediately after the required amount of hydrogen was absorbed.

5-Trimethylsilylindole (VI) was obtained from V by catalytic dehydrogenation in boiling xylene in the presence of palladium–charcoal. The reaction at lower temperature (boiling toluene) was not satisfactory.

5-Trimethylsilylgramine (VII) was obtained from VI by the Mannich reaction using formaldehyde and dimethylamine. It was converted into 5-trimethylsilyl-3-piperidinomethylindole (VIII) by reaction with piperidine (Scheme II).

(1) J. Shavel, M. von Strandtmann, and M. P. Cohen, *J. Amer. Chem. Soc.*, **84**, 881 (1962).

(2) E. Shaw and D. W. Woolley, *ibid.*, **75**, 1877 (1953).

(3) F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Org. Chem.*, **25**, 1542 (1960).

(4) Z. Pelchowicz, A. Kaluszyner, and M. Bentov, *J. Chem. Soc.*, 5418 (1961).

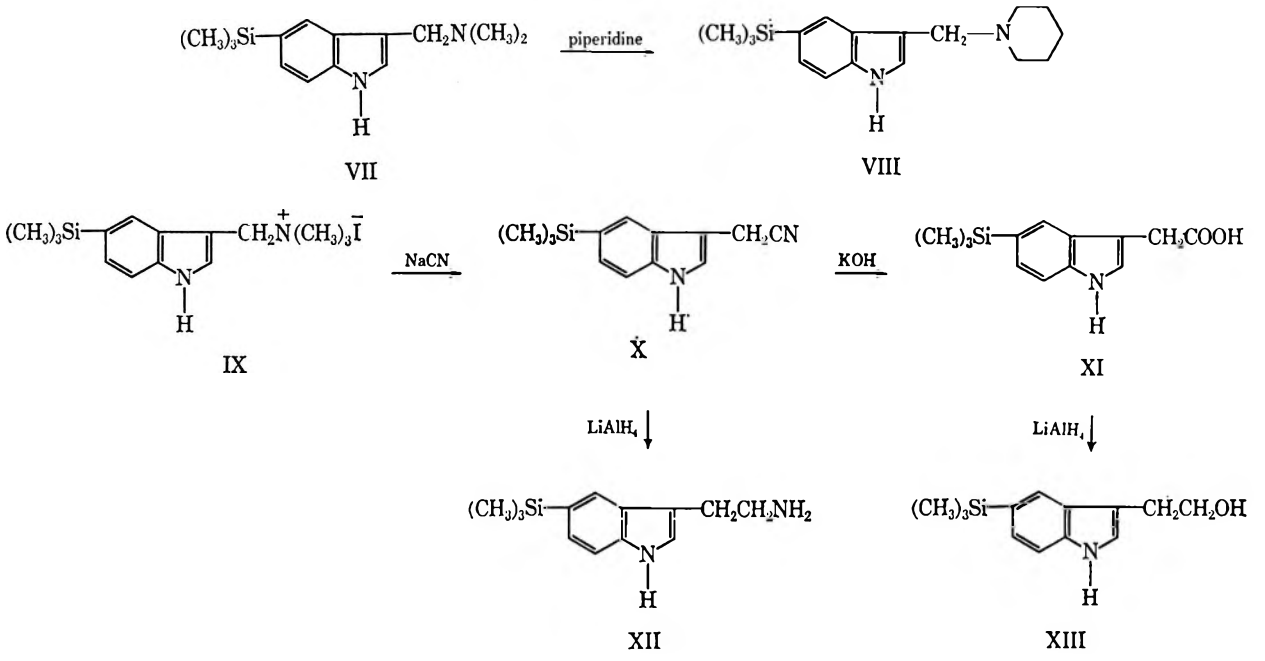
(5) J. I. DeGraw, V. H. Brown, and W. A. Skinner, *J. Med. Chem.*, **9**, 140 (1966).

(6) A. P. Terent'ev and M. N. Preobrazhenskaya, *Zh. Obshch. Khim.*, **29**, 317 (1959).

(7) R. Ikan, E. Hoffmann, E. D. Bergmann, and A. Galun, *Israel J. Chem.*, **2**, 37 (1964).

(8) A. P. Terent'ev, M. N. Preobrazhenskaya, A. S. Bobrov, and G. M. Sorokina, *Zh. Obshch. Khim.*, **29**, 2541 (1959).

SCHEME II



Reaction of VII with methyl iodide gave the methiodide IX, which on reaction with sodium cyanide gave 5-trimethylsilylindole-3-acetonitrile (X). Compound X was hydrolyzed to the acid XI and was reduced to 5-trimethylsilyltryptamine (XII) (Scheme II).

5-Trimethylsilylindole-3-acetic acid (XI) was reduced to 5-trimethylsilylindolylethanol (XIII).

Experimental Section

Melting points were determined using a Fisher-Johns apparatus. The uv spectra were carried out in ethanol (J. T. Baker Alcohol Reagent) using a Beckman DU spectrophotometer.

N-Benzylindoline (I).—Indoline (119 g, 1 mol) was added to sodium bicarbonate (105 g, 1.25 mol) in 200 ml of water and the mixture was stirred with heating to 90–95°. Benzyl chloride (127 g, 1 mol) was added dropwise during 1.5 hr, and stirring and heating was continued for an additional 3.5 hr. After cooling the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water and dried over magnesium sulfate. N-Benzylindoline was obtained in 90% yield (190 g): bp 146–149° (1 mm); $\lambda_{max}^{ethanol}$ 254 mμ (ε 10,000) and 302 (2500).

Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69; mol wt, 209.3. Found: C, 86.35; H, 7.47; N, 6.86; mol wt, 210.1 (on titration with perchloric acid in acetic acid using crystal violet as indicator).

5-Bromo-N-benzylindoline (II).—To a solution of N-benzylindoline (104.5 g, 0.5 mol) in glacial acetic acid (500 ml) under nitrogen atmosphere, a solution of bromine (80 mg, 0.5 mol) in acetic acid (250 ml) was added with stirring and external cooling during 2 hr. A heavy bluish white precipitate of 5-bromo-N-benzylindoline hydrobromide separated; it was stirred for another 15 min, filtered off, and washed thoroughly with petroleum ether (60–80°). The precipitate was added into 10% sodium hydroxide solution. The filtrate and washings were concentrated *in vacuo* and made alkaline with sodium hydroxide solution. The alkaline mixtures were combined and the amine was extracted with ether. The ethereal extracts were washed with water, dried over sodium sulfate, and distilled *in vacuo*. The 5-bromo-N-benzylindoline (124 g, 86%) distilled at 174–176° (1 mm) and solidified on cooling: mp 33° on recrystallyzation from ethanol or 2 propanol; λ_{max} 264 mμ (ε 15,000) and 313 (2600).

Anal. Calcd for $C_{15}H_{14}BrN$: C, 62.51; H, 4.90; N, 4.86. Found: C, 62.76; H, 5.03; N, 5.04.

The compound is unstable and decomposes on heating or on standing at room temperature for long periods of time. The crude material can be used in the following step.

N-Benzyl-5-trimethylsilylindoline (III).—A solution of 5-bromo-N-benzylindoline (144 g, 0.5 mol) in dry ether (200 ml) was added dropwise with stirring and cooling to lithium metal wire (7.4 g, 1.06 g-atom) in dry ether (150 ml) in an argon atmosphere. Stirring in the cold was continued for an additional 2 hr, until almost all the lithium reacted. The reaction mixture was then cooled in an ice–salt bath, and a solution of trimethylchlorosilane (60 g, 0.54 mol) in dry ether (200 ml) was dropped in with stirring. The reaction mixture was stirred in the cold for 1 hr, followed by 16 hr at room temperature, and was filtered through glass wool. The filtrate was added cautiously to cold 30% sodium hydroxide solution, so that the reaction mixture was always alkaline, and was extracted with ether. The ethereal extract was washed with water, dried, and distilled. The N-benzyl-5-trimethylsilylindoline (113 g, 80%) was collected at 179–181° (1 mm) which solidified on cooling: mp 55° (from methanol); λ_{max} 267 mμ (ε 15,800) and 299 sh (3300).

Anal. Calcd for $C_{18}H_{23}NSi$: C, 76.81; H, 8.24; N, 4.98; Si, 9.97. Found: C, 76.91; H, 8.21; N, 5.08; Si, 10.34.

N-Acetyl-5-trimethylsilylindoline (IV).—N-Benzyl-5-trimethylsilylindoline (10 g, 0.035 mol) in acetic anhydride (35 ml) was hydrogenated in a Parr apparatus (30 psi) at room temperature in the presence of 10% Pd–C (1 g). The theoretical amount of hydrogen was taken up in about 1–1.5 hr. The catalyst and precipitated material were filtered off and washed with petroleum ether. The filtrate was poured into a solution of sodium hydroxide (50 g) in crushed ice (500 g) and stirred until all the acetic anhydride was hydrolyzed. The precipitated N-acetyl-5-trimethylsilylindoline was filtered off, combined with the first precipitate, extracted with boiling ethanol, and filtered. The solution of the N-acetyl-5-trimethylsilylindoline was concentrated to a small volume and left to crystallize for 24 hr in the refrigerator. The yield was 5.1 g (61%): mp 191°; λ_{max} 262 mμ (ε 20,000), 285 (1100), and 295 (6400).

Anal. Calcd for $C_{13}H_{19}NOSi$: C, 66.91; H, 8.21; N, 6.00; Si, 12.02. Found: C, 66.85; H, 8.42; N, 6.37; Si, 12.21.

5-Trimethylsilylindoline (V).—N-acetyl-5-trimethylsilylindoline (14 g, 0.06 mol) was added to a solution of potassium hydroxide (20 g) in water (20 ml) and diethylene glycol (180 ml) and heated under reflux for 5 hr. The reaction mixture was cooled, diluted with water (600 ml), and extracted with ether. The ethereal extract was washed with water, dried over magnesium sulfate, and distilled. The 5-trimethylsilylindoline was obtained in 78% yield (9 g): bp 98–100° (1 mm); $n^{20}D$ 1.555; λ_{max} 252 mμ (ε 11,000) and 295 (2500).

Anal. Calcd for $C_{11}H_{17}NSi$: C, 69.05; H, 8.95; N, 7.32; Si, 14.67. Found: C, 68.72; H, 8.79; N, 7.23; Si, 14.38.

5-Trimethylsilylindole (VI).—A solution of 5-trimethylsilylindoline (8 g, 0.042 mol) in xylene (110 ml) was heated under reflux for 4 hr, in the presence of 10% Pd-C (0.9 g). The reaction mixture was filtered and fractionally distilled. The 5-trimethylsilylindole (6 g, 75%) distilled at 103–105° (1 mm) or at 110–114° (2 mm) and solidified to crystals: mp 42°; λ_{max} 223 mμ (ε 56,000), 274 (5600), and 293 (3500).

Anal. Calcd for $C_{11}H_{15}NSi$: C, 69.78; H, 7.98; N, 7.40; Si, 14.82. Found: C, 69.39; H, 7.89; N, 7.34; Si, 14.35.

5-Trimethylsilylgramine (VII).—A mixture of acetic acid (20 ml), dioxane (20 ml), 37% aqueous formalin solution (1.6 g), and 28% aqueous dimethylamine solution (3.2 g) was cooled to 0° in an ice bath, and 5-trimethylsilylindole (3.8 g, 0.02 mol) was dropped in slowly with stirring during 1 hr and left overnight. The reaction mixture was diluted with water to a volume of 300 ml and filtered. The filtrate was made strongly alkaline with sodium hydroxide solution, and the trimethylsilylgramine separated out as an oil which solidified on standing to yield 4.3 g (87%): mp 113° on recrystallization from petroleum ether; λ_{max} 226 mμ (ε 51,500), 282 (5300), and 292 (4200).

Anal. Calcd for $C_{14}H_{22}N_2Si$: C, 68.24; H, 9.00; N, 11.37; Si, 11.39. Found: C, 68.14; H, 9.13; N, 11.29; Si, 11.51.

5-Trimethylsilyl-3-piperidinomethylindole (VIII).—5-Trimethylsilylgramine (1 g, 0.004 mol) in piperidine (20 ml) was heated under reflux for 3 hr. Excess piperidine was removed *in vacuo*, and petroleum ether was added to the residual oil. The 5-trimethylsilyl-3-piperidinomethylindole (1 g, 86%) crystallized out: mp 126° on recrystallization from petroleum ether; λ_{max} 226 mμ (ε 50,000), 284 (5400), and 294 (4100).

Anal. Calcd for $C_{17}H_{26}N_2Si$: C, 71.27; H, 9.15; N, 9.77; Si, 9.80. Found: C, 71.11; H, 9.20; N, 9.60; Si, 9.62.

5-Trimethylsilylindole-3-acetonitrile (X).—Methyl iodide (4 ml) in petroluem ether (10 ml) was added with stirring into a solution of 5-trimethylsilylgramine (1.23 g, 0.005 mol), stirred for 30 min, and left overnight in the cold. The precipitated methiodide was filtered off, dried, and dissolved in 50% aqueous ethanol (100 ml). Sodium cyanide (3 g, 0.06 mol) was added and the solution was stirred and heated to 70–80° for 2 hr. Water (100 ml) was added and the 5-trimethylsilyl-3-indole acetonitrile was taken up in chloroform, washed with water, dried, and concentrated *in vacuo*. Petroleum ether was then added to the concentrated solution to precipitate the nitrile. A yield of 0.82 g (72%) was obtained: mp 105° on recrystallization from chloroform–petroleum ether; λ_{max} 225 mμ (ε 52,000), 283 (5500), and 283 (4100).

Anal. Calcd for $C_{13}H_{16}N_2Si$: C, 68.37; H, 7.06; N, 12.27; Si, 12.29. Found: C, 68.23; H, 6.85; N, 12.53; Si, 12.44.

5-Trimethylsilylindole-3-acetic Acid (XI).—5-Trimethylsilylindole-3-acetonitrile (1.2 g, 0.0052 mol) in ethanol (25 ml) was hydrolyzed by heating with a solution of potassium hydroxide (4.5 g) in water (15 ml) for 10 hr in a nitrogen atmosphere. The reaction mixture was cooled, diluted with water (200 ml), and filtered. The filtrate was brought to pH 7 with hydrochloric acid and left to crystallize out in the cold for several hours, yielding 1 g (77%) of 5-trimethylsilylindole-3-acetic acid: mp 110° on recrystallization from chloroform–petroleum ether; λ_{max} 229 mμ (ε 49,500), 284 (5200), and 294 (4000).

Anal. Calcd for $C_{13}H_{17}NO_2Si$: C, 63.12; H, 6.93; N, 5.66; Si, 11.34. Found: C, 62.27; H, 7.05; N, 5.39; Si, 11.62.

5-Trimethylsilyltryptamine (XII).—A solution of 5-trimethylsilylindole-3-acetonitrile (0.8 g, 3.5 mmol) in dry ether (50 ml) was added slowly with stirring into lithium aluminium hydride (2 g, 0.053 mol) in ether (80 ml), and the mixture stirred for 10 hr. Excess lithium aluminium hydride was destroyed by addition of ethyl acetate, followed by water and then by 20% sodium hydroxide solution (4 ml). The reaction mixture was filtered, the precipitate was washed thoroughly with ether, and the combined ethereal solutions were washed with water and dried over magnesium sulfate. Upon removal of the ether 5-trimethylsilyltryptamine remained as an oil which solidified on addition of petroleum ether to yield 0.59 g (78%): mp 103° on recrystallization from chloroform–petroleum ether; λ_{max} 227 mμ (ε 48,500), 285 (5000), and 295 (4000).

Anal. Calcd for $C_{13}H_{20}N_2Si$: C, 67.19; H, 8.68; N, 12.06; Si, 12.08. Found: C, 66.98; H, 8.64; N, 12.32; Si, 12.36.

β-(5-Trimethylsilylindolyl)ethanol (XIII).—A solution of 5-trimethylsilylindole-3-acetic acid (1 g, 4×10^{-3} mol) in dry ether (50 ml) was added slowly with stirring into lithium aluminium hydride (1.5 g, 0.04 mol) in ether (50 ml), and the reaction mixture was stirred for 15 hr. Excess lithium aluminium hydride was destroyed by addition of a minimal quantity of water and the reaction mixture was filtered. The precipitate was washed thoroughly with ether and the combined ethereal solutions were washed with bicarbonate solution, followed by water, and dried over magnesium sulfate. The ether was driven off *in vacuo* and the β-(5-trimethylsilylindolyl)ethanol (0.76 g, 82%) distilled at 138–142° (1 mm): λ_{max} 229 mμ (ε 42,500), 285 (4800), and 295 (3700).

Anal. Calcd for $C_{13}H_{19}NOSi$: C, 66.91; H, 8.21; N, 6.00; Si, 12.02. Found: C, 66.81; H, 8.23; N, 6.25; Si, 11.82.

A New Synthesis of 6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole

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A four-step synthesis of the anthelmintic *dl*-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole hydrochloride (tetramisole) from styrene oxide and ethylenimine is described. The key step is the reaction of α-phenyl-2-aziridineethanol with thiocyanic acid to give 2-imino-α-phenyl-3-thiazolidineethanol hydrochloride which proceeds in excellent yield.

The reported[1] broad spectrum anthelmintic activity of 6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole hydrochloride (VI) prompted the search for a new and more general synthetic route. The previous major synthesis[2] of VI involved the condensation of a phenacyl halide with 2-aminothiazoline, sodium borohydride reduction of the resultant 3-aroylmethyl-2-iminothiazolidine, and subsequent ring closure. This paper describes a new synthesis of VI starting with styrene oxide and ethylenimine.

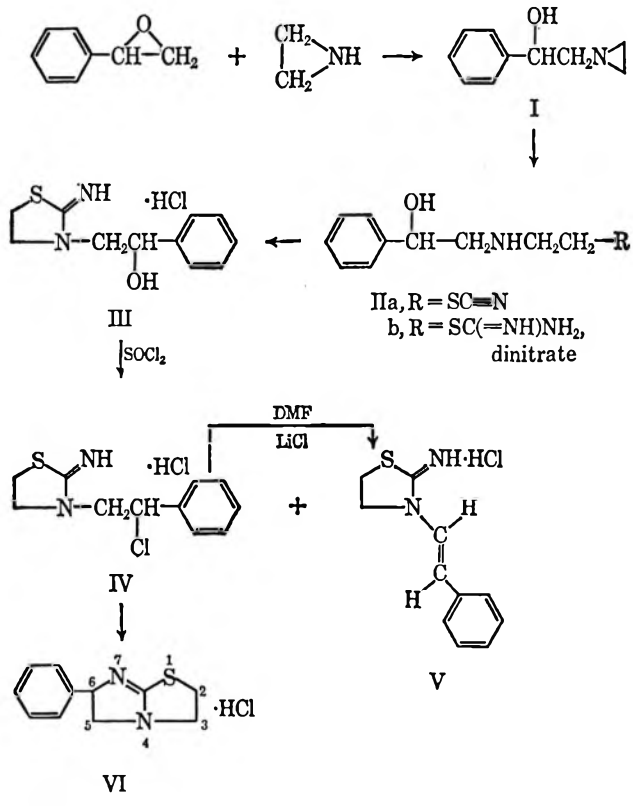
Condensation of ethylenimine and styrene oxide gave α-phenyl-1-aziridineethanol (I), which reacted with thiocyanic acid to provide 2-imino-α-phenyl-3-thiazolidineethanol hydrochloride (III). Reaction of III with thionyl chloride, followed by ring closure gave VI.

Funke and Benoit[3] obtained crystalline I in a 48% yield from the reaction of styrene oxide with ethylenimine and a trace of water in a sealed tube at 100°. Initial results in this laboratory showed that the reac-

(1) (a) D. C. I. Thienpont, O. F. J. Vanparijs, A. H. M. Raeymaekers, J. Vandenberk, P. J. A. Demoen, F. T. N. Allewijn, R. P. H. Marsboom, C. J. E. Niemegeers, K. H. L. Schellekens, and P. A. J. Janssen, *Nature*, **209**, 1084 (1966); (b) J. S. Remders, *Neth. J. Vet. Sci.*, **91**, 967 (1966); (c) J. W. Pankhurst and D. O. Sutton, *Vet. Record*, **79**, 166 (1966); J. K. Walley, *ibid.*, **78**, 406 (1966).

(2) (a) A. H. M. Raeymaekers, F. T. N. Allewijn, J. Vandenberk, P. J. A. Demoen, T. T. T. V. Offenwert, and P. A. J. Janssen, *J. Med. Chem.*, **9**, 545 (1966). (b) The route to tetramisole starting with styrene oxide and ethylenimine was independently discovered in the Research Laboratories of I.C.I.A.N.A.: A. Baklien, *et al.*, submitted for publication in *Aust. J. Chem.*

(3) A. Funke and G. Benoit, *Bull. Soc. Chim. Fr.*, 1021 (1953).



tion could be carried out without a sealed tube, and a study of the effect of solvents, temperatures, and mole ratios on the reaction rate and yield was initiated. For this purpose nmr analyses of the reaction was a convenient and rapid method of screening the effects of a wide range of variables. In the various solvent systems tested, the methine hydrogen or the X portion of an ABX system in styrene oxide appeared in the region of τ 6.2, whereas the methine hydrogen of I appeared near 5.2. Product formation could usually be calculated by integration of these two areas. In cases where the τ 5.0 region was obscured, the integrations of the methylene protons at τ 7.6 of I and of the styrene oxide methine proton were utilized.

Most significant in the variables tested was the mole ratio of ethylenimine to styrene oxide. Increasing the ethylenimine–styrene oxide ratio from equimolar to 4.5:1 resulted in large increases in product formation, with essentially no further increase at a 6:1 ratio. The presence of lower molecular weight alcohols and water in relatively low concentrations gave a definite acceleration to the reaction rate. Ethanol (in concentrations up to *ca.* 16% by weight) was found to be the most effective of these agents in increasing the rate of product formation without appreciable increases in side product formation. However, the final yield of I (as measured by nmr, gas chromatography, and distillation) was quite close to that obtained without alcohol. With other solvent systems such as pyridine, cyclohexane, decalin, chloroform, acetonitrile, acetone, water, and aqueous base the rate of product formation and/or yield was lowered. When benzene was the solvent, no reaction took place.

Similar solvent effects have been observed by Parker[4] for the reaction of styrene oxide and benzylamine. In Parker's study, varying amounts (8–40.5%) of the "abnormal" isomer in the product, resulting from amine attack at the more highly substituted carbon, were obtained. The lowest ratio of "abnormal" isomer was obtained in diethylene glycol dimethyl ether and the highest in methanol. In contrast to the results with benzylamine, the secondary amine piperidine gave only 4% of the "abnormal" isomer on reaction with styrene oxide in ethanol.[5]

In the present work, the presence of small amounts of the "abnormal" isomer, β-phenyl-1-aziridineethanol, in reaction mixtures and impure samples of I was suspected from nmr spectra.

A side reaction which was evident in the formation of I was the production of a viscous, polymeric material. References[6] to the polymerization of aziridines indicate that the reaction is catalyzed by acidic reagents. However, styrene oxide that had been specially freed from possible acidic impurities did not give results different from those obtained with commercial styrene oxide. Examination of the stability of I in various solvents revealed that styrene oxide polymerized the aziridine product. Whereas elemental analyses do not permit the polymeric distillation residue to be a polymer of I alone, they are consistent with a polymer consisting mostly of α-phenyl-1-aziridineethanol units and incorporating a small amount of styrene oxide. The styrene oxide concentration was effectively maintained at a low level by slow addition of the styrene oxide to the refluxing reaction, and by the use of a large excess of ethylenimine.

The formation of β-aminoalkylthiocyanates, which are intermediates for 2-iminothiazolidines, from β-aminoalkyl halides is of limited utility,[7] except where the halide is of the reactivity of benzyl chloride.[8] In contrast, Earley[9] has shown that ring opening of substituted aziridines to give alkyl thiocyanates is a fast reaction. The reported relative rates of thiocyanate and chloride attack on aziridinium ions indicated the feasibility of synthesizing III from I by generating thiocyanic acid from sodium thiocyanate and hydrochloric acid. This was further shown in the present work by a study of the relative rate of reaction of I with thiocyanic acid, hydrochloric acid, and various ratios of sodium thiocyanate and hydrochloric acid (Table I).

TABLE I
ACID RING OPENING OF I

Reactants (mole ratios)	% ring opened[a] after 20 min	% ring opened[a] after 60 min
I and HSCN (1:2.5)	78	>96
I, NaSCN, and HCl (1:1.5:1.5)	65	88
I, NaSCN, and HCl (1:1.5:2.5)	32	67
I and HCl (1:25)	5	10

[a] Ring opening carried out at 0° in ethanol. Residual I was determined, after quenching aliquots with base, by gas chromatography on an Aerograph gas chromatograph, Model A-90-P, with a 2-ft column packed with 6% NaOH, 10% Ucon 510 fluid on Chromosorb W diatomaceous support.

(4) R. E. Parker, *U. S. Dept. Comm., Office Tech. Serv., P B Rept.*, AD 260,659 (1961).

(5) N. B. Chapman, N. S. Isaacs, and R. E. Parker, *J. Chem. Soc.*, 1925 (1959).

(6) P. E. Fanta, "Heterocyclic Compounds with Three- and Four-Membered Rings," part 1, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 557.

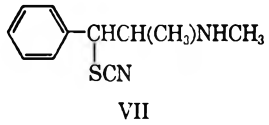
(7) A. Wolf, U. S. Patent 2,558,068 (1951); *Chem. Abstr.*, **46**, 3087e (1952).

(8) D. L. Klayman and G. W. A. Milne, *J. Org. Chem.*, **31**, 2349 (1966).

(9) J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Amer. Chem. Soc.*, **80**, 3458 (1958).

The relative rates of aziridine disappearance were shown to be clearly dependent on the thiocyanate ion concentration. Although the competing reaction of hydrogen chloride opening of I is of slight importance, a large excess of hydrochloric acid decreased the reaction rate, presumably by suppression of thiocyanic acid ionization. For synthetic preparation of III, the ideal situation for the aziridine ring-opening reaction is complete protonation of I to prevent polymerization and a large excess of thiocyanate ion during most of the reaction.

After formation of the alkyl thiocyanate IIa, extremely low pH conditions prevent ring closure to III. This may be more clearly understood by considering the thiocyanate VII which is stable in the completely protonated form, but which rapidly ring closes to give 3,4-dimethyl-5-phenyl-2-iminothiazolidine when a small amount of base is added.[7]



VII

The proper pH conditions for conversion of I into III are met by addition of the aziridine I to excess sodium thiocyanate while adjusting the reaction mixture apparent pH with hydrochloric acid.

Alternatively, the conversion of I into III could be accomplished by the reaction of I with thiourea to give the pseudothiourea IIb and subsequent ring closure of IIb in refluxing water. In this case III was conveniently isolated as the free base.

The reaction of III with thionyl chloride gave crude 3-(β-chlorophenethyl)-2-iminothiazolidine hydrochloride (IV) in good yields. The presence of minor impurity in the crude product, as demonstrated by tlc, was due to the concurrent formation of the elimination product, 2-imino-3-*trans*-styrylthiazolidine hydrochloride (V). Its structure was shown by its synthesis by hydrogen chloride elimination from IV, analyses, and spectra. In particular, the ultraviolet spectrum displayed absorbance at 295 mμ (ε 25,600) and the nuclear magnetic resonance spectrum showed two vinyl proton doublets (J = 14 cps) which confirmed the *trans*-styryl configuration.[10]

Ring closure of the free base of IV was accomplished in good yield to give VI.

Experimental Section[11]

α-Phenyl-1-aziridineethanol (I).—To 387.6 g (9.0 mol) of stirred refluxing ethylenimine was added 360.5 g (3.0 mol) of styrene oxide over a period of 170 min, and the reaction heated at reflux an additional 2 hr. The viscous residue (486.6 g), after evaporation of the ethylenimine under vacuum, was distilled at 0.35 mm to give 388.55 g (79%) of oily crystals in 3 fractions: 3.05 g, bp 25–105°, mp 56–71°; 182.7 g, bp 98–105°, mp 57–73°; 202.8 g, bp 98°, mp 57–71° [lit.[3] bp 116–117° (0.06 mm), mp 73°]. The crude product was crystallized from methyl isobutyl ketone to give 268.9 g (55%) of white crystals, mp 74–75°.

Analysis of the distillate residue from the reaction of 6 mol of ethylenimine, 2 mol of styrene oxide, and 8% ethanol gave an O/N ratio of 1.12.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58; O, 9.80. Found: C, 74.09; H, 7.99; N, 7.87; O, 10.05 (by difference).

Stability of α-Phenyl-1-aziridineethanol (I).—The stability of I in ethylenimine, chloroform, methanol, *t*-butyl alcohol, and styrene oxide as 25% solutions was measured by nmr at 50°. After 20 hr I was absent from the styrene oxide solution, but essentially unchanged in the other solvents.

2-Imino-α-phenyl-3-thiazolidineethanol Hydrochloride (III).[12]—A solution of 8.11 g (0.10 mol) of sodium thiocyanate in 125 ml of ethanol was prepared in a flask fitted with a condenser, mechanical stirrer, glass electrode, and two dropping funnels. The apparent pH of the reaction was monitored with a Heathkit pH recording electrometer, standardized at pH 7.0 with aqueous buffer. To the thiocyanate solution was added 10 ml of a solution of 18.3 ml (0.22 mol) of concentrated hydrochloric acid in 50 ml of ethanol, followed by the addition of 18.0 g, (0.11 mol) of I in 50 ml of ethanol over a period of 10 min, while maintaining the apparent pH at 1.5–3.0 during the addition of I by the addition of the remainder of the hydrochloric acid solution. After 50 min at 40–45°, the precipitated sodium chloride was filtered; the filtrate was stirred at 40–45° for 1.5 hr and overnight at room temperature. Filtration of the mixture gave 10.45 g of product, mp 201–203°. Concentration of the mother liquor at reduced pressure gave an additional 12.0 g, mp 200–204°. The yield was 87% (based on sodium thiocyanate) or 78% (based on I). The infrared spectrum showed bands at 1610 and 1660 cm^{-1}, and no absorption band in the 2000–2200-cm^{-1} region (no SC≡N).[13]

Hydrolysis of 2-acetylimino-α-phenyl-3-thiazolidineethanol[2] at room temperature for 3 days in dilute hydrochloric acid gave a low yield of analytically pure III, mp 200–201.5°. The infrared spectrum was identical with that of III prepared from I.

Anal. Calcd for $C_{11}H_{15}N_2SClO$: C, 51.06; H, 5.84; N, 10.82; S, 12.39; Cl, 13.70. Found: C, 51.22; H, 5.90; N, 10.80; S, 12.39; Cl, 13.93.

2-{2-[β-Hydroxyphenethyl]aminoethyl}-2-thiopseudourea Dinitrate (IIb).—A modification of the general procedure of Brois[14] was used.

To a stirred slurry prepared by the addition of 29 ml (0.46 mol) of 16 *N* nitric acid to 15.22 g (0.20 mol) of thiourea in 80 ml of methanol, a solution of 32.64 g (0.20 mol) of α-phenyl-1-aziridineethanol in 60 ml of methanol was added over 25 min at 7–10°. After an additional 25 min at 5–10°, the solution was evaporated at reduced pressure to give 81.14 g of yellow solid. Recrystallization from ethanol gave 55.68 g of white crystals, mp 111–118°. Recrystallization from methanol–isopropyl alcohol gave 48.83 g (67% of theory) of analytically pure product, mp 134–137°.

Anal. Calcd for $C_{11}H_{19}N_5SO_7$: C, 36.16; H, 5.24; N, 19.17; S, 8.78. Found: C, 36.41; H, 5.48; N, 19.10; S, 8.49.

2-Imino-α-Phenyl-3-thiazolidineethanol (III Free Base). Method A.—A modification of the procedure of Doherty[15] for the ring closure of S,2-aminoethylisothiouronium bromide hydrobromide was used.

A solution of 6.0 g (0.016 mol) of 2-[2-(β-hydroxyphenethylamino)ethyl]-2-thiopseudourea dinitrate in 150 ml of water was heated at reflux for 4 hr, then cooled in an ice bath and made basic with concentrated ammonium hydroxide. The resultant precipitate was filtered and washed consecutively with water, ethanol, and ether. The dried product weighed 2.1 g (58%), mp 121–123°, and was identical by infrared spectrum with the product prepared by method B.

Method B.—A mixture of 1.29 g (0.005 mol) of III and 15 ml of water was warmed and treated with ammonium hydroxide. The precipitated free base was filtered and dried to give 0.85 g (76%) of crystals, mp 125.5–126.5°.

Recrystallization of the crude product from benzene gave the

(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York. N. Y., 1959, p 85.

(11) Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained in mineral oil mull on a Perkin-Elmer Infracord spectrometer, and ultraviolet spectra by means of a Cary Model 11M spectrometer. Nuclear magnetic resonance spectra were obtained with a Varian nuclear magnetic resonance spectrometer, Model A-60. Melting points were obtained in open capillaries with a Thomas–Hoover capillary melting point apparatus and are corrected.

(12) The hydrobromide salt of III has been prepared by another route.[2]

(13) D. W. Emerson and J. K. Booth, *J. Org. Chem.*, **30**, 2380 (1965).

(14) S. J. Brois, *U. S. Dept. Comm., Office Tech. Serv., P B Rept.* 135,447; *Chem. Abstr.*, **54**, 12,090b (1960).

(15) D. G. Doherty, R. Shapira, and W. T. Burnett, Jr., *J. Amer. Chem. Soc.*, **79**, 5667 (1957).

analytical sample, mp 125–125.5°, which had an infrared spectrum identical with III free base prepared by method A.

Anal. Calcd for $C_{11}H_{14}N_2SO$: C, 59.43; H, 6.35; N, 12.60; S, 14.42. Found: C, 59.93; H, 6.60; N, 12.69; S, 14.73.

3-(β-Chlorophenethyl)-2-iminothiazolidine Hydrochloride (IV).—To a stirred slurry of 40.0 g (0.154 mol) of III and 62 ml of methylene chloride was added 17 ml (28.4 g, 0.238 mol) of thionyl chloride over a period of 2–3 min. The reaction mixture was stirred for 45 min, filtered, washed with methylene chloride and ether, and dried. The crude product weighed 30.0 g (91%): mp 178–182° and 240°; λ_{max}^{MeOH} 295 mμ. Recrystallization of the product from ethanol gave 25.3 g (59%) of white crystals, mp 245–246°. Tlc analysis (silica gel) in the solvent system acetonitrile–ammonium hydroxide (95:5, v/v) revealed a major component at R_f 0.80 and a very minor component at R_f 0.85 in both crude and recrystallized product. The minor component had the same mobility as V.

Anal. Calcd for $C_{11}H_{14}N_2SCl_2$: C, 47.66; H, 5.09; N, 10.11; S, 11.56; Cl, 25.58. Found: C, 47.06; H, 4.67; N, 9.37; S, 10.72; Cl, 23.41.

An aqueous solution of the hydrochloride was treated with sodium perchlorate to give the perchlorate salt, mp 206–207°, homogeneous by tlc.

Anal. Calcd for $C_{11}H_{14}N_2SCl_2O_4$: C, 38.72; H, 4.14; N, 8.21; S, 9.40; Cl, 20.78. Found: C, 38.90; H, 4.19; N, 8.01; S, 9.50; Cl, 21.06.

2-Imino-3-*trans*-styrylthiazolidine Perchlorate and Hydrochloride (V).—The following procedure was adapted from that used for the dehydrobromination of α-bromo ketones.[16]

A mixture of 16.0 g (0.0583 mol) of IV, 4.24 g (0.10 mol) of lithium chloride, and 130 ml of dry dimethylformamide was stirred at 113–120° for 3.5 hr, and then at room temperature for 16 hr. The mixture was poured into 1 l. of water and 450 ml of ether and ammonium hydroxide was added to a pH of 8–9. The aqueous layer was extracted again with 450 ml of ether, the ether extracts were washed with water, and dried over anhydrous potassium carbonate. Removal of the solvent *in vacuo* gave 9.43 g of a colorless oil.

The hydrochloride salt was prepared with ethanolic hydrogen chloride. The crude yellow gummy hydrochloride from evaporation of the solvent was warmed with 700 ml of water and filtered; the filtrate was treated with an aqueous solution of 7.35 g (0.06 mole) of sodium perchlorate to precipitate the perchlorate which, after filtering, washing with water, and drying under vacuum, weighed 5.83 g, mp 210–214°. Two recrystallizations from absolute ethanol gave the analytical sample, mp 232.5–234°.

Anal. Calcd for $C_{11}H_{13}N_2SClO_4$: C, 43.35; H, 4.30; N, 9.19; S, 10.52; Cl, 11.63. Found: C, 43.15; H, 4.31; N, 8.98; S, 10.67; Cl, 11.64.

The perchlorate was converted into the free base with ammonium hydroxide and extracted into chloroform. Evaporation of the chloroform, solution in methanol, and the addition of ethanolic hydrogen chloride gave the hydrochloride as cream-colored crystals, mp 224–225°. Recrystallization from methanol–ethanol gave the analytical sample as white needles, mp 223–224°. This had the same tlc mobility as the minor component of IV.

Anal. Calcd for $C_{11}H_{13}N_2SCl$: C, 54.87; H, 5.44; N, 11.64; S, 13.32; Cl, 14.73. Found: C, 54.84; H, 5.40; N, 11.62; S, 13.62; Cl, 14.96.

6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole Hydrochloride (VI).—A slurry of IV prepared from 7.77 g (0.030 mol) of III and 3.21 ml (0.045 mol) of thionyl chloride in 68 ml of methylene chloride (see the preparation of IV) was poured into ice and water and made basic by the careful addition of 3 *N* sodium hydroxide solution. The layers were separated, the aqueous layer extracted with 50 ml of methylene chloride, the organic phase washed with water, and the solvent removed at reduced pressure. The residual free base of IV was refluxed in 100 ml of isopropyl alcohol for 50 min to effect ring closure. The resultant hydrochloride precipitate was filtered, washed with ether, and dried to give 3.22 g of light yellow crystals, mp 255–259° (lit.[2] mp 260–270°). The mother liquor upon treatment with isopropyl alcoholic hydrogen chloride and concentration at reduced pressure gave an additional 2.43 g. The total crude yield was 78%. Recrystallization of the combined fractions from ethanol gave 4.30 g (59%) of product, mp 260–262°.

Registry No.—I, 15591-40-9; IIb, 15591-46-5; III, 15591-41-0; III free base, 15591-42-1; IV, 15643-70-6; IV perchlorate salt, 15643-71-7; V, 15591-43-2; V perchlorate salt, 15591-44-3; VI, 5086-74-8.

(16) (a) D. Djerassi, N. Finch, R. C. Cookson, and C. W. Bird, *J. Amer. Chem. Soc.*, **82**, 5488 (1960); (b) R. Joly and J. Warnant, *Bull. Soc. Chim. Fr.*, 367 (1958).

New Heteroaromatic Compounds. XXIX.[1] The Mechanism of Salt Formation in Some Nitroborazarophenanthrenes[2]

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Received October 10, 1967

The mechanism of salt formation in 6- and 8-nitro-10-methyl- and -10-hydroxy-10,9-borazarophenanthrene[4] has been studied, using ir and ^{11}B nmr[5] spectroscopy, and their pK_A's have been measured. These borazaro derivatives differ from most other analogous compounds[5] in that they behave as Lewis acids, salt formation involving addition of base to boron rather than loss of a proton from OH or NH. Their pK_A's are surprisingly low, comparable with that of phenol, and their longest wavelength absorption bands show large bathochromic shifts on salt formation.

In the course of another investigation, we noticed that 6- and 8-nitro-10-hydroxy-10,9-borazarophenanthrene (Ia and IIa, respectively) both developed intense colors on treatment with alkali, implying that in their conjugate bases there is an enhanced mesomeric interaction between the imino nitrogen and the nitro group *ortho* or *para* to it.

In a prior paper[4] of this series, we reported studies of salt formation in a number of compounds containing the groups BOH, using ^{11}B nmr. The results established that compounds of this type behave as Lewis acids, rather than protic acids, unless the boron atom forms part of an aromatic ring. When the boron atom does form part of an aromatic ring, as in the case in 10-hydroxy-10,9-borazarophenanthrene (IIIa), salt formation normally involves loss of a proton from the hydroxyl group. These results made it difficult to understand the behavior of Ia and IIa, for loss of a proton from hydroxyl would leave an ion (IV) in which the negative charge should be mainly localized

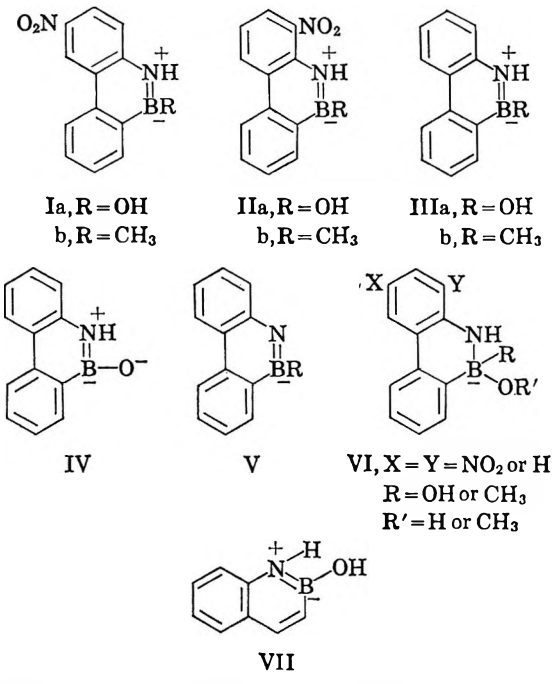
(1) Part XXVIII: M. J. S. Dewar and R. Jones, *J. Amer. Chem. Soc.*, in press.

(2) This work was supported by a grant from the Robert A. Welch Foundation.

(3) Robert A. Welch Postdoctoral Fellow.

(4) M. J. S. Dewar and V. P. Kubba, *Tetrahedron*, **7**, 213 (1959).

(5) M. J. S. Dewar and R. Jones, *J. Amer. Chem. Soc.*, **89**, 2408 (1967).



Ia, R = OH
b, R = CH_3

IIa, R = OH
b, R = CH_3

IIIa, R = OH
b, R = CH_3

IV

V

VI, X = Y = NO_2 or H
R = OH or CH_3
R′ = H or CH_3

VII

on oxygen and in which one would not therefore expect any large change in the NH–NO_2 interaction.

The position was made even more intriguing by the observation that the 10-methyl derivatives, Ib and IIb, also gave colors on treatment with alkali, which seemed to suggest that the conjugate base had lost protons from the imino groups, being nitro derivatives of the ions V. Such a reaction would, however, be surprising in the case of Ia or IIa, since it would require the proton in an imino group to be more acidic than one in hydroxyl.

We therefore measured the ^{11}B nmr spectra of I and II, both in neutral solution and in the presence of excess sodium hydroxide or sodium methoxide, with the results shown in Table I.

TABLE I

^{11}B CHEMICAL SHIFTS OF I AND II UNDER NEUTRAL AND ALKALINE CONDITIONS

Compd	Solvent	Base	Chemical shift,[a] δ	Δδ[b]	Line width at half-height, Hz
Ia	Dimethyl sulfoxide	None	−36.9		1250
		OH^-	−12.5	24.4	780
		OCH_3^-	−8.7	28.2	565
Ib	Tetrahydrofuran	None	−38.2		443
		OH^-	−20.0	18.2	394
		OCH_3^-	−11.3	26.9	283
IIb	Tetrahydrofuran	None	−41.0		380
		OH^-	−21.5	19.5	310
		OCH_3^-	−11.4	29.6	207

[a] Chemical shift in parts per million (ppm) relative to ether–boron trifluoride complex. [b] Change in chemical shift in passing from neutral to alkaline solution.

No signals could be obtained from Ia, presumably because the line was too broad; the signals for the other compounds all showed very large upfield shifts on addition of alkali, together with significant decreases in line width. These results indicate unambiguously[5] that salt formation in Ia, Ib, and IIb in each case involves addition of base to boron, rather than loss of a proton from oxygen or nitrogen, the resulting anions being of the type VI.

This conclusion was confirmed by comparisons of the ir spectra of I and II under neutral and basic conditions. The 10-hydroxy derivatives (Ia and IIa) were studied as free acids, and as salts with sodium methoxide, in potassium bromide disks. The 10-methyl derivatives (Ib and IIb) were studied using matched cells and solvents (dioxane or tetrahydrofuran) that are relatively transparent in the 3–4-kK region, with and without addition of sodium methoxide. The results are shown in Table II. In all cases, a strong NH band was observed at 3.3–3.4 kK, showing that salt formation did not involve the imino group. In the case of Ia and IIa, the BOH hydroxyl band at *ca.* 3.5 kK also persisted in the salt. For comparison, the spectrum of 10-methyl-10,9-borazarophenanthrene (IIIb) was also measured.

TABLE II

INFRARED SPECTRA OF I AND II AS FREE ACIDS AND AS SALTS

Compd	Conditions	NH stretch, K	OH stretch, K
IIIb	KBr disk	3390	
Ib	KBr disk	3370	
	Dioxane	3300	
	Dioxane–$NaOCH_3$	3310	
IIb	KBr disk	3370	
	Tetrahydrofuran	3375	
	Tetrahydrofuran–$NaOCH_3$	3376	
Ia	Ia in KBr disk	3320	3560
	Salt ($NaOCH_3$) of Ia in KBr disk	3370	3500
IIa	IIa in KBr disk	3355	3540
	Salt ($NaOCH_3$) of IIa in KBr disk	3375	3550

The proton nmr spectra of Ib and IIb were also measured under neutral and alkaline conditions, using acetone-d_6 as solvent. Progressive addition of sodium methoxide led to a progressive upfield shift of the BCH_3 resonance until a limiting value was reached, corresponding presumably to the total conversion of the parent compounds, in which boron is more or less neutral,[6] into the ions (VI) in which boron carries a formal negative charge. The magnitude of the shifts (0.9 and 1.1 ppm for Ib and IIb, respectively) again provides strong evidence that salt formation involves attachment of base to boron.

Table III records pK_A values for these compounds, together with data for the band of lowest frequency in the uv-visible spectrum. It should be added that IIIb failed to react with sodium methoxide in methanol, being, as expected, a much weaker acid than I or II.

It will be seen that salt formation leads to a very large bathochromic shift (>100 nm) and that the compounds are quite acidic, their pK_A resembling that of phenol. This is in marked contrast to simple hydroxyborazaro compounds such as IIIa or 2-hydroxy-2,1-borazaronaphthalene (VII) which are very weak acids; VII for example is not significantly more

(6) Although dipolar resonance structures are written for these compounds to emphasize their aromatic nature and relationship to phenanthrene, the net formal charge in boron is almost certainly quite small. This is indicated by the low dipole moment of 10-methyl-10,9-borazarophenanthrene (0.16 D) [R. Huisgen, I. Ugi, I. Ziegler, and H. Huber, *Tetrahedron*, **15**, 44 (1961)] and by detailed SCF MO calculations which will be reported elsewhere in due course.

TABLE III
FIRST ABSORPTION BANDS AND pK_A FOR I AND II

Compd	pK_A	Solvent for spectroscopic measurement	First absorption band P_{max}, nm	Log ϵ
IIIb		95% EtOH	327	4.014
Ib	9.65	95% EtOH	345	4.021
		95% EtOH + excess OH^-	457	4.253
IIb	9.80	95% EtOH	375	3.754
		95% EtOH + excess OH^-	514	3.954
Ia	9.64	95% EtOH	352	3.928
		95% EtOH + excess OH^-	465	4.212
IIa	9.01	95% EtOH	390	3.697
		95% EtOH + excess OH^-	495	3.939

acidic than water.[7] These results show unequivocally that there must be strong π bonding between boron and nitrogen in compounds such as III, corresponding to significant participation by the dipolar resonance structures written above, as otherwise introduction of nitro groups would not have such a large effect on the Lewis acidity of the boron, nor would salt formation by addition to boron have such a large effect on the absorption spectrum. Introduction of a nitro group leads to cross conjugation, with consequent decreases in the π-electron density on boron and in the mesomeric stabilization of the boron-containing ring; both these effects should increase the Lewis acidity of boron. Likewise addition of base to boron removes it from conjugation with the adjacent imino nitrogen, thus greatly increasing the interaction of the latter with an *ortho* or *para* nitro group. It is true that the nitro group should also indirectly increase the acidity of the hydroxylic protons in Ia or IIa by making the boron atom more positive; the change in acidity of the proton should, however, be much less than that of boron, so it is not surprising that Ia and IIa behave as Lewis acids, while IIIa behaves as a protic one.

The conclusion that the B–N π bonds in compounds such as III must be strong is not surprising in view of clear evidence that such compounds are aromatic.[8]

In conclusion, it might be remarked that the color changes shown by these compounds on treatment with base are very marked and that they might therefore prove useful as indicators; the alkaline solutions of Ia and IIa in particular are quite stable, and the color change in the case of Ia is particularly intense.

(7) R. Dietz, Ph.D. Thesis, Queen Mary College, University of London, 1960.

Experimental Section

Compounds I and II were prepared by nitration of III, and of the analogous 10-methyl derivative, as described previously,[4] these in turn being obtained by the procedure of Dewar, Dewar, and Gaibel.[9]

The pK_A measurements were carried out spectrophotometrically by the method of Perkampus and Rossel.[10]

Registry No.—Ia, 15813-11-3; Ib, 15856-52-7; IIa, 15889-55-1; IIb, 15813-12-4; IIIb, 15813-13-5.

(8) See M. J. S. Dewar, *Prog. Boron Chem.*, **1**, 235 (1964).
(9) M. J. S. Dewar, R. B. K. Dewar, and Z. L. F. Gaibel, *Org. Syn.*, **46**, 65 (1966).
(10) H. H. Perkampus and T. Rossel, *Z. Electrochem.*, **60**, 1102 (1956).

The Synthesis of 6-Substituted Thieno[3,2-*b*]pyrroles[1,2]

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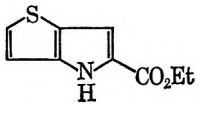
The synthetic pathway to 5-carbethoxythieno[3,2-*b*]pyrrole has been improved and a new product isolated from its reaction with formaldehyde and dimethylamine. Several 6-substituted 5-carbethoxythieno[3,2-*b*]pyrrole compounds have been hydrolyzed and decarboxylated under mild conditions to afford important intermediates for the preparation of thieno[3,2-*b*]pyrrole analogs of natural indole compounds.

In a recent paper, the preparations of 5-carbethoxythieno[3,2-*b*]pyrrole (I) and a number of its 6-substituted derivatives were reported.[4] In a continuing effort to prepare 6-substituted derivatives of thieno[3,2-*b*]pyrrole which would be analogous to naturally occurring 3-substituted indole compounds, a study of the hydrolysis and decarboxylation of several of these disubstituted thieno[3,2-*b*]pyrroles has been undertaken. Moreover, the synthetic pathway to I has been improved and a new product isolated from its reaction with formaldehyde and dimethylamine.



I

A key intermediate in the preparation of I and in the first synthesis of thieno[3,2-*b*]pyrrole[5] was 2-methyl-3-nitrothiophene (V) which was obtained in 16% over-all yield from 2,5-dibromothiophene. This same intermediate has also been prepared in 14% over-all yield from 2-methylthiophene (II) by successive chlorosulfonation, nitration, and dechlorosulfonation reactions.[6] By adapting the method of Siedel and Sturn[7] for the chlorosulfonation reaction and the method of Carpanelli and Leandri[8] for the nitration reaction, the latter process has been improved to give 2-methyl-3-nitrothiophene in

(1) Supported in part by a research grant (CA-8663) from the National Cancer Institute, U. S. Public Health Service.
(2) Abstracted in part from a thesis submitted by R. L. Keener to the Graduate College of the University of Illinois, Urbana, Ill., in partial fulfillment of requirements for the degree of Doctor of Philosophy, 1967.
(3) (a) National Science Foundation Summer Fellow, 1964; (b) Phillips Petroleum Co. Fellow, 1965–1966.
(4) W. W. Gale, A. N. Scott, and H. R. Snyder, *J. Org. Chem.*, **29**, 2160 (1964).
(5) H. R. Snyder, L. A. Carpino, F. Zack, Jr., and J. F. Mills, *J. Amer. Chem. Soc.*, **79**, 2556 (1957).
(6) C. Sone and Y. Matsuki, *Nippon Kagaku Zasshi*, **83**, 496 (1962).
(7) W. Siedel and K. Sturn, German Patent 1,088,509; *Chem. Abstr.*, **56**, 456*f* (1962).
(8) C. Carpanelli and G. Leandri, *Ann. Chim.* (Rome), **51**, 181 (1961).

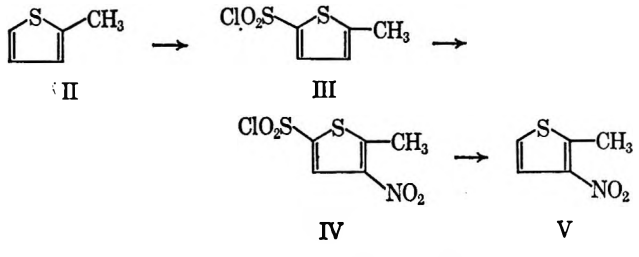
TABLE I

NUCLEAR MAGNETIC RESONANCE DATA

	Aromatic protons[a,b]			Substituent protons[a,b]	
Compd	Chemical shift (δ), ppm	Ring position	Coupling constants, cps	Chemical shift (δ), ppm	Assignment
XIII[c]	7.40 (d)	2	$J_{2,3}$ = 5.0	9.80	(—CHO)
	7.10 (d)	3	$J_{2,5}$ = 1.3		
	8.00	5			
XIV[d]	6.98 (d)	2	$J_{2,3}$ = 5.0	3.56	($CH_2N(CH_2)_5$)
	6.75 (d)	3	$J_{2,5}$ = 1.3		
	6.69	5		2.46 (m), 1.52 (m)	($CH_2N(CH_2)_5$)
XV[d]	6.95 (d)	2	$J_{2,3}$ = 5.0	3.48	($CH_2N(CH_3)_2$)
	6.76 (d)	3	$J_{2,5}$ = 1.3	2.26	($CH_2N(CH_3)_2$)
	6.72	5			
IX[d]	7.25 (d)		$J_{2,3}$ = 5.0	4.34 (q)	($CO_2CH_2CH_3$)
	6.80 (d)			1.35 (t)	($CO_2CH_2CH_3$)
				3.83	($CH_2N(CH_3)_2$)
				2.34	($CH_2N(CH_3)_2$)
XVI[d]	6.71	3	$J_{3,6}$ = 0.7	4.34 (q)	($CO_2CH_2CH_3$)
	7.08	6	$J_{4,6}$ = 1.9	1.36 (t)	($CO_2CH_2CH_3$)
				3.65	($CH_2N(CH_3)_2$)
				2.28	($CH_2N(CH_3)_2$)

[a] Spectra were determined on Varian Associates Model A-60 spectrometer using tetramethylsilane as an internal reference. [b] Letters in parentheses refer to peak multiplicity: d, doublet; t, triple; q, quartet; m, unresolved multiplet. [c] 20% in dimethyl sulfoxide-d_6. [d] 10–20% in deuteriochloroform.

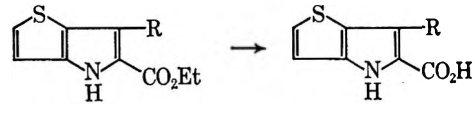
an over-all yield of approximately 50%. The chlorosulfonation and nitration reactions yielded 2-methylthiophene-5-sulfonyl chloride (III) and 2-methyl-3-nitrothiophene-5-sulfonyl chloride (IV) in yields of 63 and 91%, respectively.



II III IV V

A new product (VI) was obtained in 25% yield during the preparation of I and was subsequently converted in 70% yield into I by treatment with acid. Mass and nmr spectral data indicated that the new product was a dimer of I. The nmr spectrum of VI in dimethyl sulfoxide-d_6 (15%) exhibited three aromatic proton singlets at δ 6.60, 6.76, and 7.00. Although the last peak was found to be split by 0.8 cps when the aromatic region was expanded, the other two peaks could not be sufficiently resolved to observe fine splitting. Based on previously observed aromatic coupling constants for thieno[3,2-*b*]pyrroles,[9] the above data suggest that the dimer is formed by connection across the two thiophene rings and that the fully aromatized thienopyrrole portion of the dimer is unsubstituted at the 3 position.

Gale, Scott, and Snyder[4] obtained the Mannich bases VIII and IX from the reaction of I with formaldehyde and piperidine or dimethylamine, respectively, and converted the methiodide salt of VIII into the 6-formyl derivative VII in a modified Sommelet reaction.[4] Scott hydrolyzed VII to the carboxylic acid X but was unable to effect the decarboxylation of X or its anil derivative in hot dimethylaniline or 2-aminoethanol.[10]

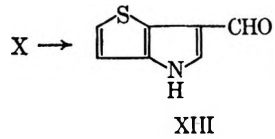


VII R = —CHO X

VIII R = —CH_2N⟨⟩ XI

IX R = —$CH_2N(CH_3)_2$ XII

A number of substituted indole-2-carboxylic acids have been decarboxylated in good yield in recent years by heating the appropriate acid with a small amount of its copper salt in quinoline[11] or dimethylacetamide.[12] When X was heated with a small amount of its copper salt in a minimum volume of two parts tetramethylurea and one part dimethylacetamide, decarboxylation occurred smoothly to give thieno[3,2-*b*]pyrrole-6-carboxaldehyde (XIII) in 60% yield. Less satisfactory yields of XIII were obtained if X was replaced by its *p*-chloroanil derivative, if either solvent was employed alone, or if the same two solvents were used in a 1:1 ratio.



XIII

The nmr spectrum (Table I) of XIII in dimethyl sulfoxide-d_6 was consistent with the structure assigned to XIII. This spectrum showed three proton signals in the aromatic region and the observed coupling constants, $J_{2,3}$ = 5.0 cps and $J_{2,5}$ = 1.3 cps, were similar to those previously reported for N-benzylthieno[3,2-*b*]-pyrrole.[9] The latter compound also exhibits a long-range coupling of approximately 0.7 cps between the 3 and 6 protons.[9]

The conversion of 6-piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (VIII) into acid XI was effected

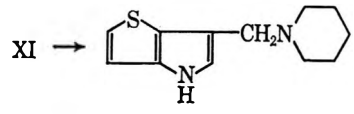
(9) R. J. Tuite, H. R. Snyder, A. L. Porte, and H. S. Gutowsky, *J. Phys. Chem.*, **65**, 187 (1961).

(10) A. N. Scott, Ph.D. Thesis, University of Illinois, Urbana, Ill., 1965.

(11) E. Piers and R. K. Brown, *Can. J. Chem.*, **40**, 561 (1961).

(12) G. Casini and L. Goodman, *ibid.*, **42**, 1235 (1964).

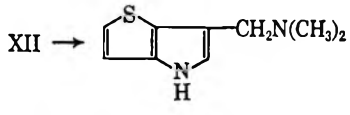
in 81% yield when VIII was heated in refluxing water for 12 hr. This acid (XI) underwent facile decarboxylation in a weakly acidic solution to afford 6-piperidinomethylthieno[3,2-b]pyrrole (XIV) in 77% yield. The



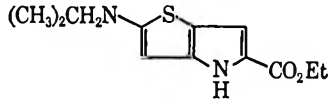
XIV

conversion of VIII into XIV was also accomplished in 58% over-all yield without isolation of the intermediate acid XI by acidifying the aqueous solution after hydrolysis and by heating the acidified solution to reflux until carbon dioxide evolution ceased. The hydrolysis of VIII also could be achieved by saponification with dilute sodium hydroxide in 50% aqueous ethanol. No decarboxylated product was obtained when XI was subjected to the same conditions of decarboxylation which afforded the maximum yield of the 6-formyl compound XIII. The structure of XIV was indicated by its nmr spectrum (Table I) in deuteriochloroform which showed three aromatic proton signals whose observed coupling constants $J_{2,3}$ = 5.0 cps and $J_{2,5}$ = 1.3 cps were also in agreement with those values previously reported for N-benzylthieno[3,2-b]pyrrole.[9]

Similarly, when chromatographically pure 6-dimethylaminomethyl-5-carbethoxythieno[3,2-b]pyrrole (IX) was heated in refluxing water for 6 hr and the solution subsequently acidified and refluxed until carbon dioxide evolution ceased, 6-diethylaminomethylthieno[3,2-b]-pyrrole (XV) was obtained in an over-all yield of 50%. The structure of XV was also indicated by its nmr spectrum (Table I) in deuteriochloroform which showed aromatic proton resonance and coupling constants almost identical with those found for XIV.



XV



XVI

When the crude product obtained from the reaction of I with formaldehyde and dimethylamine was recrystallized once from methylcyclohexane and then subjected to the same conditions of hydrolysis employed for the Mannich bases VIII and IX, a new product (XVI) was isolated in 70% yield. The nmr spectrum (Table I) of XVI in deuteriochloroform was similar to that reported[4] for IX except that the thiophene AB system of protons was replaced by singlets at δ 6.71 (β-thiophene proton) and at 7.08 (β-pyrrole proton). Moreover, the peak at δ 7.08 showed a primary coupling of 1.9 cps attributed to interaction between the 4 and 6 protons,[4,9] and a secondary coupling of 0.7 cps with the peak at 6.71; since the magnitude of the latter coupling has been shown to be characteristic of interaction between the 3- and 6-protons of thieno[3,2-b]-pyrroles,[9] XVI has been tentatively identified as 2-dimethylaminomethyl-5-carbethoxythieno[3,2-b]pyrrole.

Both XVI and I were recovered in good yields when they were heated in refluxing water for 12–24 hr. Moreover, the fact that pure IX was converted into the acid XII rather than into XVI when it was heated in refluxing water indicates that XVI is not an artifact of IX. Indeed, both nmr spectral data and thin layer chromatography indicated that the once-recrystallized product from the preparation of IX was a mixture of IX and XVI. The former compound could be readily eluted from an acid-washed alumina column with an ethanolic benzene solution, but the latter compound could not be eluted from the column in a pure form. The above data suggest that the major product of the reaction of I with formaldehyde and dimethylamine is XVI rather than IX and that the major product of the reaction when piperidine is used in place of dimethylamine is VIII, as originally reported.[4]

The preceding hydrolysis studies also suggest, but do not establish, that the hydrolysis of the Mannich bases VIII and IX in water may be intramolecularly catalyzed, possibly by involvement of the tertiary nitrogen atom of these compounds. It has recently been reported, for example, that a tertiary nitrogen atom intramolecularly catalyzes the solvolysis of some ceveratrum alkaloid esters.[13]

Experimental Section[14]

2-Methylthiophene-5-sulfonyl Chloride (III).—To 88 ml of chlorosulfonic acid at 0–5° was added with stirring and in small portions 112 g of phosphorus pentachloride. The solution was warmed to 10° and maintained at 10–15° while 40 g of 2-methylthiophene was added dropwise to the stirred solution. After the addition was completed, the deep red solution was rapidly, but cautiously, poured onto 1 kg of ice with vigorous stirring.

This mixture was then extracted with two cold 500-ml portions of chloroform. The chloroform extracts were washed with 300 ml of water and dried over anhydrous sodium sulfate. The wash water was reextracted with 200 ml of chloroform and the organic layer combined with the original chloroform extracts. The chloroform was removed from the dried, filtered solution on a rotary evaporator to afford 72 g of a black tarry residue which was distilled *in vacuo*. There was obtained 50.4 g (63%) of 2-methylthiophene-5-sulfonyl chloride, bp 94–97° (0.6–0.7 mm) [lit.[6] bp 96–98° (0.5 mm)].

2-Methyl-3-nitrothiophene-5-sulfonyl Chloride (IV).—A solution of 15 ml of acetic anhydride and 20 ml of fuming nitric acid (sp gr, 1.5) was cooled to 0° and was maintained below 5° while a solution of 6 g of 2-methylthiophene-5-sulfonyl chloride in 15 ml of acetic anhydride was added dropwise with stirring. The solution was poured onto 50 g of crushed ice 45 min after the addition had been completed. The white crystalline solid was collected on a Büchner funnel and dried *in vacuo* over phosphorus pentoxide to yield 6.64 g (91%) of 2-methyl-3-nitrothiophene-5-sulfonyl chloride, mp 75–76° (lit.[6] mp 75.5–76°).

2-Methyl-3-nitrothiophene (V).—This compound was prepared from IV in 92% yield by the method of Sone and Matsuki.[6] The observed melting point was 44–45.5° (lit.[6] mp 75–76°).

$C_{18}H_{18}N_2O_4S_2$ (VI).—This substance was isolated as a major by-product in the preparation of 5-carbethoxythieno[3,2-b]pyrrole. A solution of 546 g of stannous chloride dihydrate in 922 ml of concentrated hydrochloric acid was added to a stirred solution of 74 g of ethyl 3-nitro-2-thienylpyruvate[4] in 800 ml of absolute ethanol. The addition took 4 hr and the reaction temperature

(13) S. M. Kupchan, S. P. Eriksen, and Y.-T. S. Liang, *J. Amer. Chem. Soc.*, **88**, 347 (1966).

(14) Melting points were determined on a Kofler heating stage apparatus and are uncorrected. Microanalyses were performed by Mr. J. Nemeth and his associates. Mass spectral determinations were made by Mr. J. Wrona on an Atlas Model CH 4 mass spectrometer. Infrared spectra were determined on a Perkin-Elmer Model 512 infrared spectrophotometer, and nuclear magnetic resonance (nmr) spectra were determined on a Varian Associates Model A-60 nuclear magnetic resonance spectrometer by members of the Spectroscopy Laboratory of the University of Illinois.

was maintained below 30° during this time. After the addition was completed, the heterogeneous reaction mixture was stirred at room temperature for 12 hr. A tan precipitate was filtered from the reaction solution and dried over phosphorus pentoxide to yield 10.0 g of crude VI. The filtrate was extracted with a total of 2.5 l. of methylene chloride and the latter washed successively with 1.5 l. of 6 *N* HCl, 1.2 l. of water, and 1.2 l. of saturated sodium chloride solution. The methylene chloride extracts were dried over anhydrous sodium sulfate and the solvent was removed *in vacuo* to yield 41 g of a black residue. This residue and the original 10 g of precipitate were purified by chromatography on columns of acid-washed alumina. Initial elution of the columns with benzene afforded 23.9 g (50%) of pure 5-carbethoxythieno[3,2-*b*]pyrrole, mp 131–133° (lit.[4] mp 132–133°). Subsequent elution of the columns with chloroform yielded 11.8 g (25%) of the dimeric product VI. Recrystallization of this solid from 95% ethanol yielded VI as white needles, mp 191–192°. A mass spectrum of this solid run at low ionization voltage gave a parent ion peak at *m/e* 390. An infrared spectrum of the product in a potassium bromide disk showed broad carbonyl absorption centered at 1670 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}N_2O_4S_2$: C, 55.43; H, 4.65. Found: C, 55.27; H, 4.61.

Conversion of VI into 5-Carbethoxythieno[3,2-*b*]pyrrole (I).—A solution of 7.0 g of VI and 2.0 g of *p*-toluenesulfonic acid in 300 ml of toluene was refluxed for 3 hr under a nitrogen atmosphere. The dark red solution was cooled to room temperature, washed once with 10% sodium bicarbonate solution and twice with deionized water. The toluene layer was dried over anhydrous sodium sulfate, filtered onto a column of acid-washed alumina and the column eluted with benzene to afford 4.7 g (67%) of 5-carbethoxythieno[3,2-*b*]pyrrole, identified by the mixture melting point method and by thin layer chromatography.

The dimer (VI) was also converted into I in 64% yield by stirring a mixture of 5 g of the former, 750 ml of concentrated hydrochloric acid and 3 l. of absolute ethanol for 96 hr at room temperature. The product was obtained by extraction with methylene chloride and purified by chromatography on a column of acid-washed alumina using benzene as the eluting solvent.

6-Formyl-5-carboxythieno[3,2-*b*]pyrrole (X).—A heterogeneous solution containing 3.03 g of 6-formyl-5-carbethoxythieno[3,2-*b*]-pyrrole[4] in 61 ml of 10% aqueous sodium hydroxide was refluxed for 2 hr. The basic solution was cooled, filtered, and acidified with 3 *N* HCl to precipitate the product which was collected and washed with water. The yield of crude acid after drying *in vacuo* over phosphorus pentoxide was 2.11 g (80%). An analytical sample was prepared by one recrystallization from absolute ethanol, mp 218° dec (lit.[10] mp 220° dec).

Anal. Calcd for $C_8H_5NO_3S$: C, 49.22; H, 2.58; N, 7.18. Found: C, 49.27; H, 2.47; N, 6.86.

The *p*-chloroanil derivative of 6-formyl-5-carboxythieno[3,2-*b*]pyrrole (X) was prepared by adding a solution of 65 mg of *p*-chloroaniline in 5 ml of ethanol to a warm solution of 100 mg of X in 10 ml of absolute ethanol. The resulting solution was refluxed for 30 min, cooled in an ice bath and filtered, and the precipitate was collected and air dried. Recrystallization of this precipitate from absolute ethanol afforded 131 mg (84%) of the *p*-chloroanil derivative of X as yellow prisms, mp 220° dec.

Anal. Calcd for $C_{14}H_9N_2O_2SCl$: C, 55.18; H, 2.95; N, 9.20. Found: C, 55.21; H, 3.03; N, 8.90.

Thieno[3,2-*b*]pyrrole-6-carboxaldehyde (XIII).—Dry nitrogen gas was passed through a solution of 5.2 ml of N,N-dimethylacetamide (DMA) and 10.4 ml of N,N,N′,N′-tetramethylurea (TMU) for 2 hr. Lines for admitting and exiting the nitrogen gas were attached to the top of the reflux condenser and the exit line was led to a saturated barium hydroxide solution. To the DMA and TMU in the reaction flask were added 2.1 g (13.9 mmol) of 6-formyl-5-carboxythieno[3,2-*b*]pyrrole (X) and 0.21 g of the copper salt of X, prepared in 89% yield by the method of Piers and Brown.[11]

The reaction mixture was heated at 190–200° until carbon dioxide evolution was complete (*ca.* 4 hr) and then cooled to room temperature. This mixture was poured onto 100 ml of crushed ice, heated to 70° on a steam bath, and filtered. The precipitate was saved, while the filtrate was cooled in an ice bath, acidified to pH 5 with 1 *N* HCl, and extracted with five volumes of diethyl ether. The ether was removed *in vacuo* and the residue triturated with a small amount of very dilute HCl solution. The solid which formed was collected, washed with cold water, and dried over phosphorus pentoxide *in vacuo* to afford 1.258 g (69%) of slightly impure thieno[3,2-*b*]pyrrole-6-carboxaldehyde (XIII), mp 146–149°. Recrystallization of part of this material from water afforded 0.434 g of XIII as white prisms, mp 149–150°. Sublimation of the remainder of this material and of the original precipitate at 100° (0.05 mm) yielded an additional 0.545 g of XIII, mp 148–149°. The total yield of XIII was 0.924 g (60%). A sample of the product recrystallized from water showed aldehydic carbonyl absorption at 6135 cm^{-1} in its infrared spectrum (KBr disk) and was submitted for microanalysis.

Anal. Calcd for C_7H_5NOS: C, 55.61; H, 3.33. Found: C, 55.41; H, 3.25.

XIII was similarly prepared and isolated from a number of smaller scale reactions in which the amount of reactants and the amount and ratio of solvents were varied. In one series of experiments, in which all reaction conditions were identical except that the ratio of DMA/TMU employed was 1:0, 0:1, and 1:2 gave XIII in yields of 23, 22, and 37% respectively. The time required for complete decarboxylation in DMA was found to be approximately twice that required in pure TMU. Moreover, over the ranges of concentration examined, the yield of product was found to increase consistently as the total volume of solvent in these reactions was decreased.

An analogous series of studies on the *p*-chloroanil derivative of X consistently gave lower yields of XIII than those obtained from X, apparently because of greater difficulty in isolating the decarboxylated product in these experiments and converting it into XIII.

6-Piperidinomethyl-5-carboxythieno[3,2-*b*]pyrrole (XI).—A mixture of 5 g of 6-piperidinomethyl-5-carbethoxythieno[3,2-*b*]-pyrrole (VIII)[4] and 1.8 l. of water was refluxed for 12 hr. The solution was cooled, filtered to remove a trace of solid, and evaporated to dryness *in vacuo*. Recrystallization of the residue from absolute ethanol afforded 3.6 g (81%) of 6-piperidinomethyl-5-carboxythieno[3,2-b]pyrrole as a tan granular solid, mp 218–220° dec. Carbonyl absorption appeared at 1600 cm^{-1} in the infrared spectrum of this product in a potassium bromide disk.

Anal. Calcd for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.59. Found: C, 58.58; H, 6.10; N, 10.16.

6-Piperidinomethylthieno[3,2-*b*]pyrrole (XIV). A. From 6-piperidinomethyl-5-carboxythieno[3,2-*b*]pyrrole (XI).—A solution of 2.00 g of XI in 50 ml of water was acidified to pH 5 with dilute HCl solution and refluxed under a nitrogen atmosphere until carbon dioxide evolution ceased (*ca.* 24 hr). During this period, dilute HCl solution was periodically added to the refluxing solution in order to maintain the pH at 4–5. Carbon dioxide evolution was followed by passing the exit gases through a saturated barium hydroxide solution.

After the reaction was complete, the solution was cooled to room temperature and made alkaline with 10% sodium hydroxide solution and the precipitate extracted into 250 ml of ether. The dried (over anhydrous sodium sulfate) extracts were concentrated *in vacuo* to yield a tan solid. This solid was recrystallized from methylcyclohexane and decolorized with Darco to afford 1.3 g (77%) of 6-piperidinomethylthieno[3,2-*b*]pyrrole (XIV) as white needles, mp 136–138°. The infrared spectrum (KBr disk) of this product showed no carbonyl absorption.

Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.71. Found: C, 65.90; H, 7.34; N, 12.44.

B. From 6-Piperidinomethyl-5-carbethoxythieno[3,2-*b*]pyrrole (VIII).—A mixture of 1.25 g of VIII and 400 ml of water was refluxed under nitrogen for 12 hr. The heterogeneous solution was filtered and the filtrate reduced to 20 ml *in vacuo*. The aqueous solution after another filtration was acidified with 1 *N* HCl to pH 3 and refluxed under a nitrogen atmosphere for 60 hr. The pH was periodically adjusted to a pH of 3–4 during this time by the addition of 1 *N* HCl. By using the isolation procedure described above in paragraph A, 0.548 g (58% based on VIII) of 6-piperidinomethylthieno[3,2-*b*]pyrrole was obtained. The product melted at 135–138° and its infrared spectrum was identical with that of the product obtained in the reaction described in paragraph A.

A 58% yield of XIV was also obtained in a similar run except that the hydrolysis was carried out by refluxing a solution of 0.584 g (2 mmol) of VIII and 0.200 g (5 mmol) of sodium hydroxide in 16 ml of 50% aqueous ethanol for 5 hr. The solution was reduced in volume to remove ethanol, diluted to 100 ml with water, and decarboxylated as described in the previous paragraph. An analytical sample of the product after two recrystallizations from methylcyclohexane melted at 138–140°.

Anal. Calcd for $C_{12}H_{16}N_2S$: C, 65.41; H, 7.32; N, 12.71. Found: C, 65.46; H, 7.18; N, 12.53.

6-Dimethylaminomethylthieno[3,2-b]pyrrole (XV).—A suspension of 0.750 g of chromatographically pure 6-dimethylaminomethyl-5-carbethoxythieno[3,2-b]pyrrole (IX),[4] mp 94–95°, in 500 ml of water was refluxed for 6 hr. Since no significant precipitate formed when this cloudy solution was cooled to 0°, the solution was concentrated to 100 ml, cooled to room temperature, and filtered. The light tan filtrate was acidified to pH 5 with 3 *N* HCl solution and subjected to the same conditions of decarboxylation used for XI. After the ether extracts had been dried over anhydrous sodium sulfate, the ether was removed *in vacuo* to leave 375 mg of crude product which was recrystallized from methylcyclohexane and decolorized with Darco to afford 270 mg (50%) of 6-dimethylaminomethylthieno[3,2-b]pyrrole as buff-colored prisms, mp 117–120°. An infrared spectrum (KBr disk) of this product showed no carbonyl absorption.

Anal. Calcd for $C_9H_{12}N_2S$: C, 59.86; H, 6.71; N, 15.53. Found: C, 60.21; H, 6.89; N, 15.30.

2-Dimethylaminomethyl-5-carbethoxythieno[3,2-b]pyrrole (XVI).—The crude product obtained from the reaction of I with formaldehyde and dimethylamine by the method of Gale, Scott, and Snyder[4] was recrystallized once from methylcyclohexane. A 5.0-g sample of this material, mp 90–92°, was suspended in 1.8 l. of water and the aqueous mixture refluxed for 6 hr. When this solution was filtered hot to remove traces of solid and cooled to 0° in an ice bath, a white crystalline precipitate formed which was collected on a Büchner funnel and recrystallized from methylcyclohexane to afford 3.5 g (70%) of XVI as white needles, mp 132–133°. A mass spectrum of this product run at low ionization voltage showed a parent ion peak at *m/e* 252, as expected for an isomer of IX. An infrared spectrum of XVI in chloroform was similar to that of IX, but the two spectra were not superimposable.

Anal. Calcd for $C_{12}H_{16}N_2O_2S$: C, 57.12; H, 6.39; N, 11.10. Found: C, 57.45; H, 6.51; N, 10.50.

When 200 mg of XVI was suspended in 100 ml of water and the resulting suspension was refluxed for 6 hr, the solution became homogeneous. Upon cooling of this solution to 0°, 194 mg (97%) of XVI, mp 131–133°, precipitated.

When 3.0 g of the once-recrystallized product from the preparation of IX was placed on a column of acid-washed alumina 28 cm in height and 3.5 cm in diameter and the column was eluted with a 50% ethanolic benzene solution, only 750 mg (25%) of pure 6-dimethylaminomethyl-5-carbethoxythieno[3,2-b]pyrrole (IX), mp 94–95°, was obtained. Subsequent elution of the column failed to yield any pure material.

Attempted Hydrolysis of 5-Carbethoxythieno[3,2-b]pyrrole (I).—A mixture of 0.292 g of 5-carbethoxythieno[3,2-b]pyrrole and 150 ml of water was refluxed for 24 hr. The solution was cooled to room temperature and extracted with an equal volume of diethyl ether. The ether extract was dried over anhydrous sodium sulfate and filtered, and the ether was removed on a rotary evaporator to yield 0.215 g (74%) of 5-carbethoxythieno[3,2-b]pyrrole, mp 132–133° (lit.[4] mp 132.5–133°). The recovered material had the same R_f value as that of the starting material when compared by tlc.

Registry No.—VI, 15819-12-2; IX, 15811-13-9; X, 15811-14-0; X p-chloroanil derivative, 16315-46-1; XI, 15811-16-2; XIII, 15811-17-3; XIV, 15811-18-4; XV, 15811-19-5; XVI, 15811-20-8.

The Synthesis of Polycyclic Fused [1,2-a]Pyrroles

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The condensation of 2,5-dimethoxytetrahydrofuran with 2-amino-5-chlorobenzophenone and its two oxime forms afforded the 2-(1-pyrrolyl)benzophenone derivatives **4**, **5**, and **6**. These compounds were converted into the corresponding 2-substituted Mannich bases by treatment with formaldehyde and dimethylamine. Subsequent quaternization with methyl iodide followed by heating led to intramolecular condensations to give the pyrrolo[1,2-a]quinoline **8**, the pyrrolo[1,2-a]benzoxadiazocine **13**, and the pyrrolo[1,2-a]benzodiazepine **14**, respectively. Compound **6** with electrophiles in acid gave pyrrolo[1,2-a]quinazolines. Attempted formylation of **6** with dimethylformamide–phosphorus oxychloride yielded the pyrrolo[1,2-a]quinoxaline **21**.

The ready availability of *o*-aminobenzophenones[1] has, in the past few years, led to the synthesis of several heterocyclic systems. Thus, quinazolines,[2] benzodiazepines,[3] quinolones,[4] and indoles[5] have all been prepared from various *o*-aminobenzophenones.

As an extension of this work, and employing 2-amino-5-chlorobenzophenone **1** and its *syn*- and *anti*-oximes (**2** and **3**, respectively[6]) as starting materials, we wish to report a general synthetic approach for the preparation of derivatives of fused [1,2-a]pyrrolo quinolines, quinazolines, benzodiazepines, benzoxadiazocines, and quinoxalines.

Using the method of Clauson-Kaas for the synthesis of 1-substituted pyrroles,[7,8] compounds **1**, **2**, and **3** were treated with 2,5-dimethoxytetrahydrofuran to give the corresponding 2-(1-pyrrolyl)benzophenone derivatives **4**, **5**, and **6**, respectively (Scheme I).

The ketone **4** was then treated with formaldehyde and dimethylamine to give the corresponding Mannich base. This compound was not isolated, but alkylated with methyl iodide to give directly the quaternary salt **7** (Scheme II). When a solution of **7** in aqueous dimethylformamide was then treated with sodium cyanide, trimethylammonium iodide was displaced by cyanide ion and the carbonyl function underwent intramolecular cyclization to give the pyrrolo[1,2-a]-quinoline, compound **8**.

Similar treatment of the oximes **5** and **6** with formaldehyde and dimethylamine gave the Mannich bases **9** and **10**, respectively (Scheme III), which were also alkylated with methyl iodide to afford the corresponding quaternary salts **11** and **12**. When a solution of

(1) (a) L. H. Sternbach, E. Reeder, O. Keller, and W. Metlesics, *J. Org. Chem.*, **26**, 4488 (1961); (b) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *ibid.*, **27**, 3781 (1962).

(2) (a) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Amer. Chem. Soc.*, **82**, 475 (1960); (b) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **30**, 3957 (1965).

(3) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *ibid.*, **27**, 3788 (1962).

(4) R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 3097 (1964).

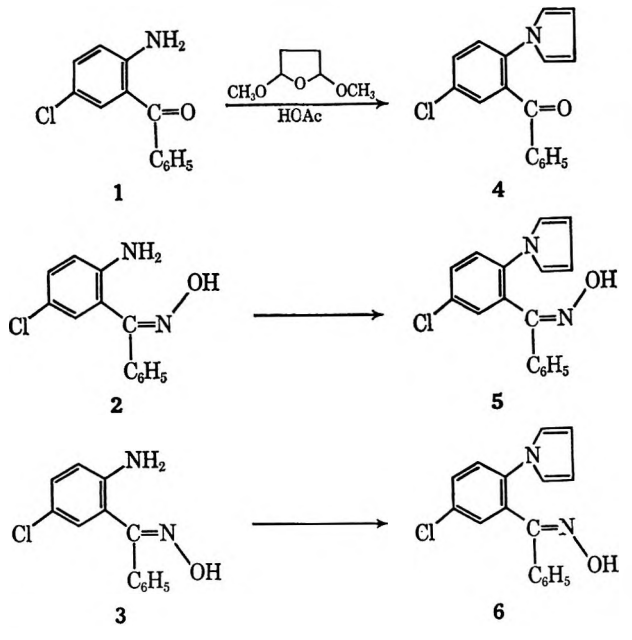
(5) R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967).

(6) The *syn* isomer is defined as that isomer in which the hydroxy group is *syn* to the phenyl ring bearing the 2-amino group. See, also, A. Stempel, I. Douvan, E. Reeder, and L. H. Sternbach, *ibid.*, **32**, 2417 (1967), footnote 7.

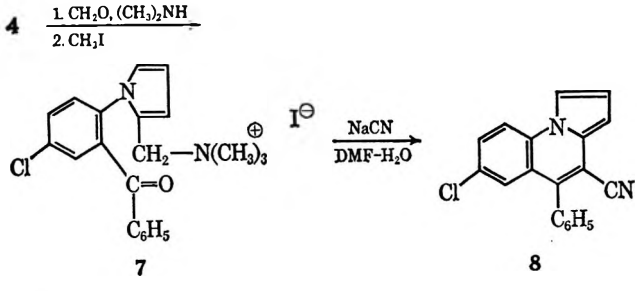
(7) (a) N. Clauson-Kaas and Z. Tyle, *Acta Chem. Scand.*, **6**, 667 (1952); (b) E. Elming and N. Clauson-Kaas, *ibid.*, **6**, 867 (1952).

(8) A. D. Josey and E. L. Jenner [*J. Org. Chem.*, **27**, 2466 (1962)] recognized the potential of this reaction in the synthesis of a pyrrolo[1,2-a]indole.

SCHEME I



SCHEME II



either of these latter compounds in dimethylformamide was warmed on the steam bath, intramolecular condensation took place with the loss of trimethylamine hydriodide to afford, from **11**, the pyrrolo[1,2-*a*]-benzoxadiazocine **13** and, from **12**, the pyrrolo[1,2-*a*]-benzodiazepine **14**.[9] (This is a further example of the O-alkylation of a *syn*-oxime and the N-alkylation of an *anti*-oxime.[7,10]) Phosphorus trichloride readily converted **14** into the corresponding desoxy derivative **15** and this was then converted into the tetrahydro derivative **16** by treatment with lithium aluminum hydride.

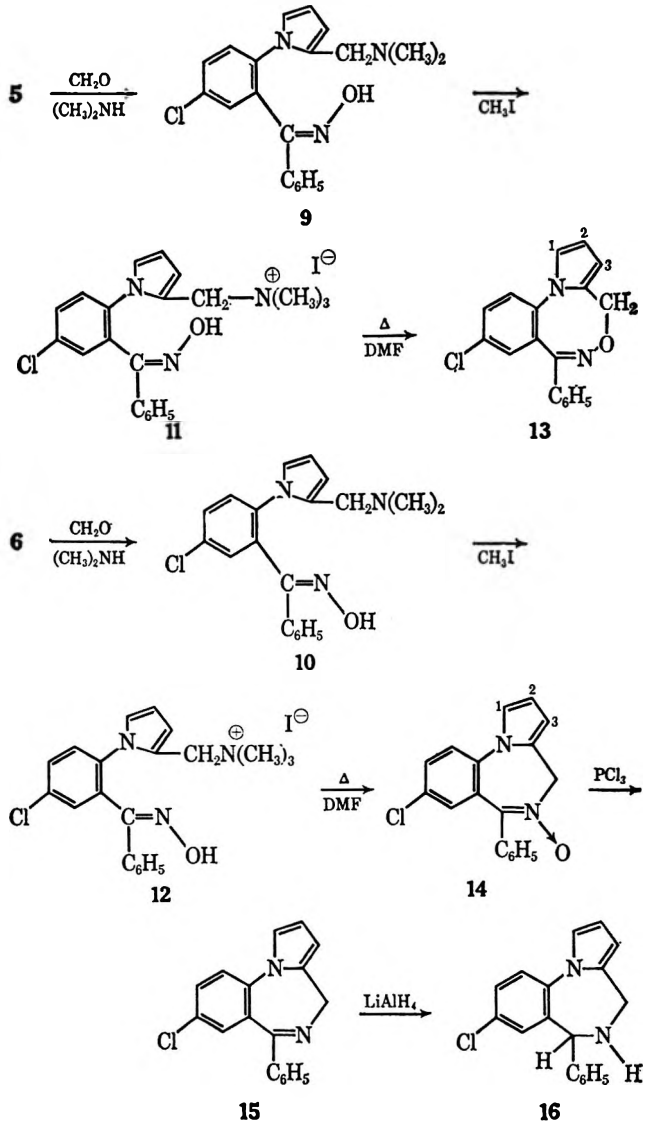
As a further extension of reactions which would convert the *anti*-oxime **6** into tricyclic products, we investigated the behavior of this substance with electrophiles in acidic media. Thus, we found that treatment of compound **6** with a molar equivalent of bromine in acetic acid at room temperature gave a bromine-free substance to which we have assigned the phenylpyrrolo[1,2-*a*]quinazoline 4-oxide structure **17** (Scheme IV). The N-oxide structure was established both by its mass spectrum which in addition to the parent ion (294) showed the strong loss of **16** (278, parent less oxygen) characteristic of N-oxides,[11] and by its conversion into the desoxy derivative **18** with hydrogen and Raney nickel. The formation of **17** from **6** may be envisioned as proceeding *via* a brominated dihydro

(9) For a discussion of condensation reactions of pyrrole Mannich bases, see H. Hellmann and G. Opitz, "α-Aminoalkylierung," Verlag Chemie, G.m.b.H., Weinheim, Berstr., Germany, 1960.

(10) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

(11) T. A. Bryce and J. R. Maxwell, *Chem. Commun.*, 206 (1965).

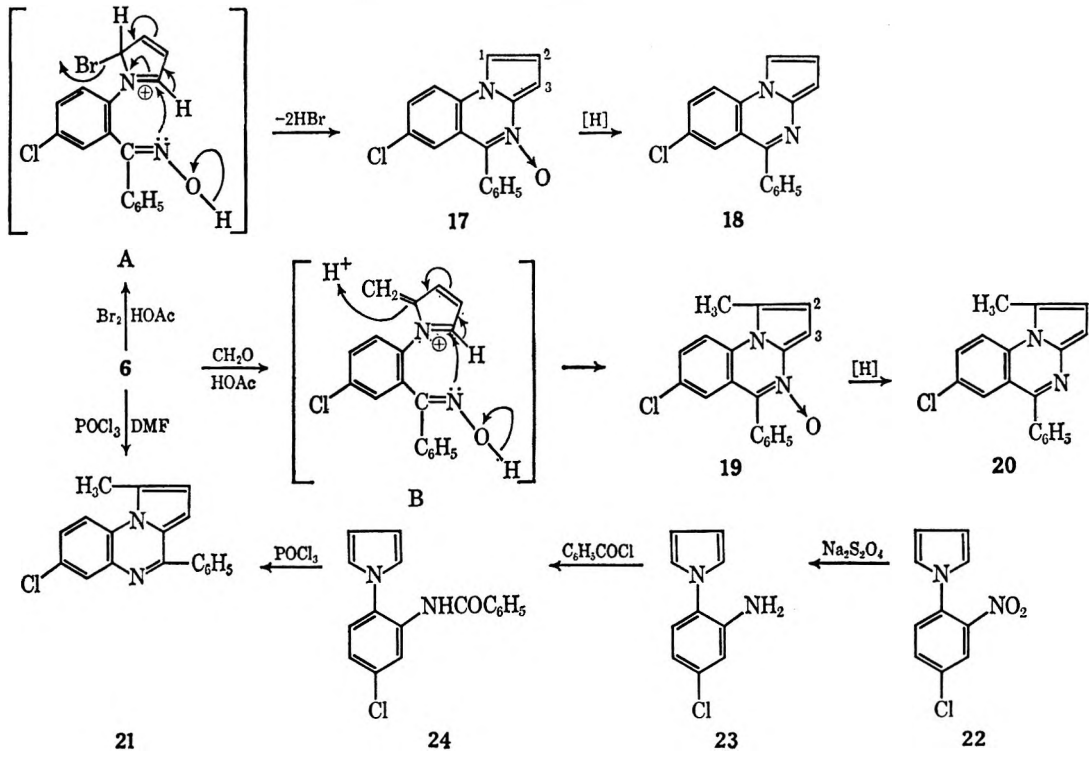
SCHEME III



intermediate such as A, which could cyclize with the elimination of bromide ion as shown (Scheme IV), to give the final product. A similar reaction sequence was observed when we treated an acetic acid solution of **6** with formaldehyde. In this instance, we isolated 7-chloro-1-methyl-5-phenylpyrrolo[1,2-*a*]quinazoline 4-oxide (**19**). The methyl substituent was assigned at position 1 and not at 3 on the basis of the nmr spectrum and also by analogy with the site of alkylation observed in the conversion of **6** into **10**. Reduction of **19** with Raney nickel gave the corresponding desoxy derivative **20**. The formation of **19** can be rationalized by a pathway analogous to that given for the formation of **17**, *i.e.*, *via* an intermediate such as B.

In an attempt to formylate one of the pyrrole oximes, **6** was treated together with a mixture of phosphorus oxychloride and dimethylformamide. Instead of the anticipated product, we obtained the pyrrolo[1,2-*a*]-quinoxaline **21**. In addition to compatible spectra, the structure of **21** was confirmed by the following synthesis. A solution of 4-chloro-2-nitroaniline in acetic acid was treated with dimethoxytetrahydrofuran to give the nitrophenylpyrrole **22**. Reduction of **22** with sodium hydrosulfite yielded the amino compound **23** which was then acylated with benzoyl chloride to give **24**. Treatment of **24** with boiling phosphorus

SCHEME IV



oxychloride gave **21**, identical in all respects with the product obtained by the attempted Vilsmeier reaction.[12] The formation of **21** from **6** would appear to be the result of a Beckmann type of rearrangement catalyzed by phosphorus oxychloride. Thus, compound **6** could then be converted into the amide **24**, which under the reaction conditions would cyclize to the quinoxaline **21**.

Experimental Section[13]

5-Chloro-2-(1-pyrrolyl)benzophenone (4).—To a solution of 41.8 g (0.18 mol) of 2-amino-5-chlorobenzophenone (**1**) in 200 ml of glacial acetic acid was added 21.4 g (0.20 mol) of dimethoxytetrahydrofuran. After heating on the steam bath for 25 min, the solution was poured into 800 ml of water and extracted with carbon tetrachloride. The addition of 10% sodium hydroxide facilitated the separation of the layers. The organic phase was separated, washed with brine, dried over sodium sulfate, and concentrated to a dark brown oil. This residue was covered with 600 ml of hexane, heated to boiling, and filtered while hot from some undissolved oil (discarded). The hexane filtrate was concentrated to small volume and cooled. The precipitated oily solid was recrystallized several times from hexane to yield 23.4 g (46%) of colorless prisms: mp 86–87°; infrared absorption ($CHCl_3$) at 1665 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29; N, 4.97. Found: C, 72.24; H, 4.43; N, 5.09.

5-Chloro-2-(1-pyrrolyl)benzophenone *syn*-Oxime (5).—A solution of 45 g (0.18 mol) of 2-amino-5-chlorobenzophenone *syn*-oxime[14] (**2**) in 200 ml of glacial acetic acid was treated with 26.5 g (0.2 mol) of dimethoxytetrahydrofuran, heated on the steam bath for 25 min, and poured into 500 ml of water. The mixture was extracted with benzene and the organic layer was separated, washed with water, dried over sodium sulfate, and concentrated to dryness. This residue was dissolved in a small amount of hot carbon tetrachloride and refrigerated. Filtration gave 27 g (50%) of the product as a cream-colored solid, mp 146–148°. Recrystallization from carbon tetrachloride yielded white plates: mp 146–147° (sintered prior to melting); ultraviolet maximum (2-propanol) at 250 mμ (ε 23,500).[15]

Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.80; H, 4.42; N, 9.44. Found: C, 69.06; H, 4.47; N, 9.49.

5-Chloro-2-(1-pyrrolyl)benzophenone *anti*-Oxime (6).—A solution of 45 g (0.18 mol) of 2-amino-5-chlorobenzophenone *anti*-oxime[16] (**3**) in 200 ml of glacial acetic acid was treated with 26.5 g (0.2 mol) of 2,5-dimethoxytetrahydrofuran and heated on the steam bath for 15 min. The reaction mixture was cooled to room temperature, poured into 500 ml of water, and extracted with benzene. The organic layer was separated, aided by the addition of 10% sodium hydroxide, washed with water, dried over anhydrous sodium sulfate, and concentrated to dryness. The residue was covered with a small amount of carbon tetrachloride, heated on the steam bath until a solid began to separate, and then refrigerated. Filtration gave 25 g (46%) of a cream-colored solid, which softened from 130° until completely melted at 168: ultraviolet maxima (2-propanol) at 227 mμ (infl) (ε 22,700) and 250 mμ (sh) (ε 19,600).[17]

Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.80; H, 4.42; N, 9.44. Found: C, 69.07; H, 4.31; N, 9.41.

7-Chloro-4-cyano-5-phenylpyrrolo[1,2-a]quinoline (8).—To a cooled, stirred solution of 20 g (0.068 mol) of **4** in 225 ml of glacial acetic acid was added 13.2 g (0.16 mol) of 37% formaldehyde followed by 28.8 g (0.16 mol) of 25% dimethylamine in water. The solution was stirred overnight at room temperature and poured into 600 ml of water. The mixture was filtered to separate a small amount of undissolved solid (discarded) and the filtrate was basified with sodium hydroxide and extracted with ethyl acetate. The organic layer was separated, washed with water, dried over sodium sulfate, and concentrated to a viscous oil. This oil was dissolved in ether and, while stirring, was treated with 20 ml of methyl iodide. A precipitate formed

(12) The cyclization of 1-(2-acylaminophenyl)pyrroles as a facile, general method for the preparation of pyrrolo[1,2-a]quinoxalines has been reported by G. W. H. Cheeseman and B. Tuck [*J. Chem. Soc.*, 852 (1966)].

(13) All melting points are corrected. Infrared spectra were determined using a Beckman IR-9 spectrophotometer, nmr spectra with a Varian A-60 spectrometer, mass spectra with a CEC 21-100 spectrometer, and ultraviolet spectra with a Cary Model 14 spectrophotometer. The dimethoxytetrahydrofuran used in these experiments was obtained from the Aldrich Chemical Co.

(14) The ultraviolet spectrum indicated that the starting material was contaminated with less than 1% of the *anti* isomer. The characteristic differences in the ultraviolet spectra of pairs of oximes has been reported by J. G. Pritchard, G. F. Field, K. Koch, G. Raymond, L. H. Sternbach, and S. Traiman [*Appl. Spectry.*, **20**, 363 (1966)].

(15) The ultraviolet spectrum of this material is vastly different from that of the starting material but very similar to that observed for 2-methylbenzophenone *syn*-oxime. For an interpretation of these differences, see ref 14.

(16) This material was shown to be contaminated with less than 4% of the *syn* isomer by ultraviolet spectroscopy (*cf.* ref 14).

(17) This absorption is about the same as that observed with 2-methylbenzophenone *anti*-oxime.

immediately. After standing at room temperature for 3 hr, the solid was filtered to give 30.9 g (94%) of **7** as a cream-colored solid. Recrystallization of a small sample from methanol–ether gave off-white prisms, mp 165° with slow decomposition. Upon vacuum drying the sample turned green and consequently satisfactory microchemical data could not be obtained for this substance.

To a solution of 150 ml of water in 350 ml of dimethylformamide was added 25 g (0.052 mol) of **7** and 25 g (large excess) of sodium cyanide. After being heated on the steam bath for 8 hr, the mixture was poured into 1.5 l. of water and filtered. The precipitate was washed with water and dissolved in benzene. After drying, the benzene was concentrated to dryness and the residue triturated with a small amount of hot 2-propanol and refrigerated. Filtration gave 2.6 g (17%) of **8** as yellow-green crystals, mp 180–183°. The analytical sample was recrystallized from 2-propanol to yield bright, yellow plates: mp 182–183°; infrared absorption ($CHCl_3$) at 2225 cm^{-1} (CN); ultraviolet maxima (2-propanol) at 240 mμ (ε 36,700), 252 (32,500), 259 (34,000), 288 (11,000), 299 (9200), 327 (sh) (1250), 343 (2700), 360 (4000), and at 406 (5200).

Anal. Calcd for $C_{19}H_{11}ClN_2$: C, 75.37; H, 3.66; N, 9.25. Found: C, 75.39; H, 3.56; N, 9.42.

5-Chloro-2-(2-dimethylaminomethyl-1-pyrrolyl)benzophenone *syn*-Oxime (9).—To an ice-cooled, sitrred solution of 29.7 g (0.1 mol) of **5** in 300 ml of glacial acetic acid was added 22.2 g (0.2 mol) of 37% formaldehyde and 45 g (0.2 mol) of 25% dimethylamine in water. After stirring for 22 hr at room temperature, the solution was poured into 800 ml of water and basified with 20% sodium hydroxide. The precipitate was filtered, washed with water, and recrystallized from methanol–acetone to yield 23.7 g (66%) of white crystals, mp 203–204° dec.

Anal. Calcd for $C_{20}N_{20}ClN_3O$: C, 67.84; H, 5.70; N, 11.81. Found: C, 68.03; H, 5.77; N, 11.66.

5-Chloro-2-(2-dimethylaminomethyl-1-pyrrolyl)benzophenone *anti*-Oxime (10).—To an ice-cooled, stirred solution of 29.67 g (0.1 mol) of **6** in 300 ml of acetic acid was added 22.2 g (0.2 mol) of 37% formaldehyde and then, portionwise, 45 g (0.2 mol) of 25% dimethylamine in water. After stirring at room temperature for 20 hr, the solution was poured into 700 ml of water, basified with concentrated ammonia, and extracted with ethyl acetate. The organic layer was separated, washed with water, dried over sodium sulfate, and concentrated to dryness. The residue was recrystallized from methanol to give 20.8 g (58%) of white crystals, mp 173–179°. An additional recrystallization from methanol gave colorless prisms: mp 175–179°; nmr peaks ($CDCl_3$) at δ 5.72, 5.84, 6.35 (3 H, ABX pattern, pyrrole H's 5, 4, and 3, had respectively, $J_{3,4}$ = 3.5 cps, $J_{4,5}$ = 2.8 cps, and $J_{3,5}$ = 1.7 cps).[18]

Anal. Calcd for $C_{20}H_{20}ClN_3O$: C, 67.84; H, 5.70; N, 11.81. Found: C, 67.80; H, 5.50; N, 11.95.

5-Chloro-2-(2-dimethylaminomethyl-1-pyrrolyl)benzophenone *syn*-Oxime Methyl Iodide (11).—To a stirred solution of 13.8 g (0.039 mol) of **9** in 150 ml of tetrahydrofuran was added 11 g (0.078 mol) of methyl iodide. After stirring for 3 hr at room temperature, the suspension was refrigerated overnight. Filtration and recrystallization of the product from methanol–ether gave 17 g (88%) of white crystals, mp 145–155° dec.

Anal. Calcd for $C_{21}H_{23}ClIN_3O$: C, 50.87; H, 4.68; N, 8.48. Found: C, 50.66; H, 4.70; N, 8.18.

5-Chloro-(2-dimethylaminomethyl-1-pyrrolyl)benzophenone *anti*-Oxime Methyl Iodide (12).—A mixture of 13 g (0.036 mol) of **10** and 50 ml of methyl iodide was stirred at room temperature for 15 min, 100 ml of ether was added, and the suspension was allowed to stand for an additional 3.5 hr. Filtration yielded 17 g (95%) of off-white colored crystals, mp 140–146°. Recrystallization from methanol–ether gave white needles, mp 140–145° (foamed).

Anal. Calcd for $C_{21}H_{23}ClIN_3O$: C, 50.87; H, 4.68; N, 8.48. Found: C, 50.47; H, 4.76; N, 8.36.

9-Chloro-7-phenyl-4H-pyrrolo[1,2-*a*][4.1.5]benzoxadiazocine (13).—A solution of 40 g (0.085 mol) of **11** in 150 ml of dimethylformamide was heated on the steam bath for 2.5 hr under nitrogen. The solution was poured into water, stirred for 15 min, and filtered. The precipitate was collected, dried at room temperature, and then extracted with 400 ml of hot benzene. The benzene solution, filtered from 16.5 g of unreacted starting material, was washed with water, dried over sodium sulfate, and concentrated. The residual orange oil was triturated with 10 ml of 2-propanol and scratched to induce crystallization. The solid was collected and recrystallized twice from 2-propanol to give 7.8 g (50%, based upon starting material consumed) of tan rods: mp 137–138.5°; nmr peaks ($CDCl_3$) at δ 6.70, 6.18, 6.08 (3 H, ABX pattern, pyrrole H's 1, 2, 3, respectively)[19] and at 5.38 (2 H, AB quartet, J = 14 cps, CH_2).

Anal. Calcd for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24; N, 9.07. Found: C, 70.06; H, 4.31; N, 9.09.

8-Chloro-6-phenyl-4H-pyrrolo[1,2-*a*][1,4]benzodiazepine 5-Oxide (14).—A solution of 18 g (0.036 mol) of **12** in 80 ml of dimethylformamide was heated under nitrogen on the steam bath for 3 hr and then poured into 300 ml of water. The precipitate was filtered, washed with water, and dissolved in benzene (a small amount of undissolved residual oil was discarded). The benzene extract was washed with water, dried over sodium sulfate, and concentrated. The residue was dissolved in chloroform and filtered over 75 g of alumina[20] with the aid of additional chloroform. The eluate was treated with Darco G charcoal and filtered and the filtrate concentrated to an orange oil. The oil was crystallized from a small amount of 2-propanol to give 4.4 g (40%) of orange-brown crystals, mp 180–186°. The analytical sample was recrystallized from 2-propanol–methylene chloride to give chunky, pale orange prisms: mp 191–193° (sintered at 185°); nmr peaks ($CDCl_3$) at δ 6.42 (2 H doublet, J = 2 cps, pyrrole H's 2 and 3), at 7.15 (1 H multiplet J = 2 cps, pyrrole H 1), and at 5.07 (2 H singlet, CH_2).

Anal. Calcd for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24; N, 9.07. Found: C, 70.30; H, 4.44; N, 8.89.

8-Chloro-6-phenyl-4H-pyrrolo[1,2-*a*][1.4]benzodiazepine (15).—To a solution of 7 g (0.022 mol) of **14** in 150 ml of chloroform was added 3.6 ml (0.042 mol) of phosphorus trichloride. The solution was heated under reflux for 30 min and poured into 300 ml of 1 *N* sodium hydroxide. The organic phase was separated, washed with brine, and dried over sodium sulfate. This solution was filtered through 150 g of alumina and the alumina washed with chloroform until the eluate was colorless. Evaporation of the solvent gave a reddish oil which was covered with 275 ml of hexane, heated to reflux, and filtered while hot to remove some oily solid (discarded). The filtrate was concentrated to 85 ml and refrigerated. Filtration gave 3.6 g of amber crystals, mp 122–124°. Concentration of the filtrate gave an additional 0.3 g of product to yield 3.9 g (61%). The analytical sample was recrystallized from hexane to give pale, amber prisms: mp 125–126°; nmr peaks (DMSO-d_6) at δ 7.33, 6.28, 6.17 (3 H, ABX pattern, pyrrole H's 1, 2, 3, respectively, $J_{1,2}$ = 3 cps, $J_{2,3}$ = 3.5 cps, $J_{1,3}$ = 1.5 cps), and 4.52 (2 H, AB quartet, J = 13 cps, CH_2).

Anal. Calcd for $C_{18}H_{13}ClN_2$: C, 73.84; H, 4.48; N, 9.57. Found: C, 74.11; H, 4.32; N, 9.63.

8-Chloro-5,6-dihydro-6-phenyl-4H-pyrrolo[1,2-*a*][1.4]benzodiazodiazepine (16).—To a suspension of 3.5 g of lithium aluminum hydride in 200 ml of tetrahydrofuran was added 11.8 g of **15**. After refluxing overnight a few milliliters of aqueous tetrahydrofuran was added slowly and the mixture was filtered. The solution was concentrated and the resultant oil recrystallized several times from a large volume of hexane to give tan rods: mp 145–146°; nmr peaks ($CDCl_3$) at δ 6.95, 6.30, 6.17 (3 H, ABX pattern, pyrrole H's 1, 2, 3, respectively, $J_{1,2}$ = 3 cps, $J_{2,3}$ = 3.5 cps, $J_{1,3}$ = 1.5 cps), and 3.81 (2 H, AB quartet, J = 15 cps, CH_2).

Anal. Calcd for $C_{18}H_{15}ClN_2$: C, 73.34; H, 5.13; N, 9.50. Found: C, 73.55; H, 5.35; N, 9.62.

7-Chloro-5-phenylpyrrolo[1,2-*a*]quinazoline 4-Oxide (17).—To a stirred solution of 3 g (0.01 mol) of **6** in 500 ml of glacial acetic acid was added dropwise 1.8 g (0.011 mol) of bromine and the resultant mixture stirred for 2 hr at room temperature. The resultant suspension was filtered to give a brown solid, which rendered water strongly acidic to pH paper. This solid was stirred in excess 1 *N* sodium hydroxide for a few minutes, filtered, and then thoroughly washed with water. After trituration with a small amount of acetone the product was recrystallized twice from carbon tetrachloride to give 1.5 g (50%) of pale yellow prisms: mp 226–229° dec (changed to needles *ca.* 200°); ultraviolet maxima (2-propanol) at 241 mμ (ε 29,250), 252 (infl) (31,500), 256 (32,500), 282 (18,250), 343 (infl) (5200), 360

(18) For a listing of pyrrole coupling constants, see S. Gronowitz, *et al.*, *Ark. Kemi*, **18**, 133 (1961).

(19) The J values for these pyrrole hydrogens were not clearcut within 1 cps.

(20) Alumina refers to Woelm alumina, activity I.

(6600), and 385 (sh) (6200); nmr peaks (DMSO-d_6) at δ 5.17 (2 H doublet, J = 2.5 cps, pyrrole H's 2 and 3) and at 8.22 (1 H triplet, J = 2.5 cps, pyrrole H 1).

Anal. Calcd for $C_{17}H_{11}ClN_2O$: C, 69.27; H, 3.76; N, 9.50. Found: C, 69.72; H, 3.81; N, 9.49.

7-Chloro-5-phenylpyrrolo[1,2-a]quinazoline (18).—A solution of 4.7 g (0.015 mol) of **17** in 100 ml of dioxane was shaken under 1 atm of pressure and 24° in an atmosphere of hydrogen using *ca.* 6 g of Raney nickel as catalyst. After the uptake of hydrogen reached 359 ml (theory 370 ml), the mixture was filtered and the catalyst washed with 50 ml of dioxane and 50 ml of methanol. Evaporation of the solvent gave a yellow oil which crystallized upon standing. After several recrystallizations from ethanol, yellow needles were obtained, mp 149–150°.

Anal. Calcd for $C_{17}H_{11}ClN_2$: C, 73.25; H, 3.98; N, 10.05. Found: C, 72.96; H, 4.02; N, 9.93.

7-Chloro-1-methyl-5-phenylpyrrolo[1,2-a]quinazoline 4-Oxide (19).—A solution of 12 g (0.04 mol) of **6** in 100 ml of acetic acid was treated with 6 g (0.074 mol) of 37% formaldehyde and the mixture was allowed to stir at room temperature for 24 hr. The solution was poured into 300 ml of water and extracted with chloroform. The organic layer was separated (aided by the addition of alkali to the aqueous phase), washed with water, dried over sodium sulfate, and passed through 250 g of Florisil.[21] The Florisil was washed with chloroform and the eluate concentrated to dryness. The residue was dissolved in hot carbon tetrachloride and filtered from a small amount of undissolved solid (discarded); the filtrate was refrigerated. Filtration yielded 3 g (24%) of pale orange crystals: mp 220–223° dec; mass spectrum (m/e), 308 (p), 292 (p − 16); nmr peaks ($CDCl_3$) at δ 6.55, 7.05 (2 H, AB quartet, J = 4 cps, pyrrole H's 2 and 3),[22] and 2.97 (3 H singlet, CH_3).

Anal. Calcd for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24; N, 9.07. Found: C, 70.32; H, 4.19; N, 9.26.

7-Chloro-1-methyl-5-phenylpyrrolo[1,2-a]quinazoline (20).—A solution of 3 g (0.01 mol) of **19** in a mixture of 25 ml of methanol and 50 ml of dioxane was shaken under 1 atm of pressure at 24° in an atmosphere of hydrogen using 6.5 g of Raney nickel as a catalyst. After the uptake of hydrogen reached 231 ml, the mixture was filtered and the filtrate concentrated to a viscous, yellow oil. This oil, which contained some starting material (determined by tlc), was dissolved in carbon tetrachloride and placed on 150 g of alumina. Elution with 1:1 ethyl acetate–hexane gave, upon evaporation, a yellow solid which was recrystallized from ethanol to give yellow prisms, mp 139–141°.

Anal. Calcd for $C_{18}H_{13}ClN_2$: C, 73.84; H, 4.48; N, 9.57. Found: C, 73.92; H, 4.68; N, 9.44.

7-Chloro-4-phenylpyrrolo[1,2-a]quinoxaline (21). A. From 6.—To 4 g (0.055 mol) of dimethylformamide, cooled in ice, was added dropwise with stirring, 8.5 g (0.055 mol) of phosphorus oxychloride. After stirring for 15 min at room temperature, 25 ml of ethylene dichloride was added and the solution cooled to 5°. A suspension of 15 g (0.05 mol) of **6** in 60 ml of ethylene dichloride was then added portionwise during 1 hr. After stirring at room temperature for 20 min, the mixture was refluxed for 15 min and then hydrolyzed at room temperature by the dropwise addition of a solution of 37.5 g of sodium acetate trihydrate in 50 ml of water. The resultant mixture was heated to gentle reflux for 15 min and then the organic layer was separated. The aqueous phase was extracted with ether and the organic layers were combined, washed, dried over sodium sulfate, and concentrated to a dark brown solid. Trituration with hot ethanol gave 6.1 g of yellow solid, mp 150–159°. This solid was dissolved in methylene chloride and passed through 100 g of Florisil. After eluting with *ca.* 750 ml of additional methylene chloride, evaporation gave 5.4 g (38%) of product as a pale yellow solid, mp 152–155°. The analytical sample was recrystallized from methanol–methylene chloride to give pale yellow needles: mp 154–156°; ultraviolet maxima (2-propanol) at 215 mμ (infl) (ϵ 2600), 233 (27,000), 247 (infl) (35,000), 250 (36,300), 271 (23,400), 279 (infl) (2000), 327 (infl) (5900), 343 (8000), and 355 (8250); nmr peaks ($CDCl_3$) at δ 7.82, 6.80, 6.96 (3 H, ABX pattern, pyrrole H's 1, 2, and 3, respectively, $J_{1,2}$ = 2.7 cps, $J_{2,3}$ = 4.1 cps, $J_{1,3}$ = 1.3 cps).[23]

(21) Florisil (Floridin Co.) is a synthetic magnesium silicate adsorbent.

(22) The value for the spin coupling constant for these pyrrole hydrogens is consistent with the $J_{3,4}$ noted for 2,5-disubstituted pyrroles (*cf.* ref 18).

Anal. Calcd for $C_{17}H_{11}ClN_2$: C, 73.25; H, 3.98; N, 10.05. Found: C, 73.54; H, 3.84; N, 9.98.

B. From 5′-Chloro-2′-(1-pyrrolyl)benzanilide (24).—A solution of 2.6 g of **24**, prepared as described below, in 18 ml of redistilled phosphorus oxychloride was refluxed for 20 min. The excess phosphorus oxychloride was removed at reduced pressure and the residue treated with water and then basified with sodium carbonate. After extraction with chloroform, the organic phase was separated, washed, dried, and concentrated to an oil. This oil was dissolved in benzene and filtered over 80 g of alumina and the alumina washed with *ca.* 700 ml of benzene. Removal of the solvent gave a pale yellow solid, mp 150–153°. This product was identical in all respects (infrared spectra and mixture melting point) with the substance obtained from procedure A.

1-(4-Chloro-2-nitrophenyl)pyrrole (22).—A solution of 17.2 g (0.1 mol) of 4-chloro-2-nitroaniline in 100 ml of glacial acetic acid was treated with 18.8 g (0.15 mol) of dimethoxytetrahydrofuran and then heated on the steam bath for 30 min. The hot solution was filtered from a small amount of undissolved solid (discarded) and the filtrate poured into 500 ml of water. After extraction with carbon tetrachloride, the organic phase was separated, washed, dried, and filtered over 100 g of Florisil. Continued elution with carbon tetrachloride gave, upon concentration, an orange oil. The oil was dissolved in ethyl ether and the solution diluted with petroleum ether (bp 30–60°). After refrigeration, filtration gave 15.6 g (70%) of yellow-amber crystals, mp 53–54°. Recrystallization from ether–petroleum ether raised the melting point to 55–56°. The product was light sensitive becoming dark red upon exposure to overhead light.

Anal. Calcd for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.58. Found: C, 53.79; H, 3.15; N, 12.87.

1-(4-Chloro-2-aminophenyl)pyrrole (23).—To a stirred solution of 10 g (0.045 mol) of **22** dissolved in a mixture of 200 ml of tetrahydrofuran and 100 ml of water was added, portionwise, 10 g of sodium hydrosulfite. After heating on the steam bath for 5 min, an additional 10 g of sodium hydrosulfite was added. The mixture was again placed on the steam bath for 5 min after which it was treated with 23 g of additional sodium hydrosulfite and a solution of 200 ml of ethanol in 250 ml of water. After 5 min of further heating the organic solvents were removed at reduced pressure; the resultant precipitate was filtered and washed with water. Recrystallization from hexane gave 4.5 g (46%) of white needles, mp 87–88°.

Anal. Calcd for $C_{10}H_9ClN_2$: C, 62.34; H, 4.71; N, 14.54. Found: C, 62.59; H, 4.76; N, 14.59.

5′-Chloro-2′-(1-pyrrolyl)benzanilide (24).—To a solution of 6 ml of benzoyl chloride in 30 ml of pyridine, cooled in ice, was added 6.1 g (0.03 mol) of **23**. The resultant mixture was heated gently on the steam bath for 1 hr and the excess pyridine removed at reduced pressure. The residue was covered with water and the mixture extracted with ethyl ether. The organic layer was separated, washed twice with 50-ml portions of 2 *N* hydrochloric acid and with water, and then dried over sodium sulfate. Removal of the ether gave a sticky, brown solid which was recrystallized from ethanol to give 4 g (45%) of cream-colored needles, mp 124–125.5°.

Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.80; H, 4.42; N, 9.44. Found: C, 68.81; H, 4.17; N, 9.50.

Registry No.—**4**, 15707-36-5; **5**, 15893-36-4; **6**, 15707-37-6; **8**, 15707-38-7; **9**, 15707-39-8; **10**, 15707-40-1; **11**, 15707-41-2; **12**, 15707-42-3; **13**, 15707-44-5; **14**, 15707-43-4; **15**, 15707-45-6; **16**, 15707-46-7; **17**, 15707-47-8; **18**, 15814-72-9; **19**, 15814-73-0; **20**, 15814-75-2; **21**, 15814-74-1; **22**, 15893-38-6; **23**, 15814-76-3; **24**, 15893-37-5.

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(23) Similar nmr data for a series of 4-substituted pyrrolo[1,2-a]quinoxalines have been reported by G. W. H. Cheeseman and B. Tuck [*J. Chem. Soc.*, 1164 (1967)].

Derivatives of Thiacyclobutenes (Thietes). III.[1] Synthesis of Highly Unsaturated Thiete Sulfones[2,3]

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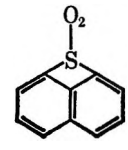
Condensations of 3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-dioxide with benzaldehyde, *p*-chlorobenzaldehyde, and *p*-methoxybenzaldehyde yield thiete sulfones which are unsaturated at every position. *p*-Nitrobenzaldehyde reacts anomalously. Reduction of the 2-benzylidene derivative by lithium aluminum hydride at −70° occurs with reduction of the double bond but not the sulfone group to give 2-benzyl-3,8-diphenyl-2H-naphtho-[3,2-*b*]thiete 1,1-dioxide admixed with starting sulfone from which it could not be separated. The large difference in chemical shift between the diastereomeric methylene protons of this compound is attributed to restricted rotation.

The α hydrogens of sulfones are acidic,[4] and condensation reactions occur between α-sulfonyl anions and carbonyl groups.[5]

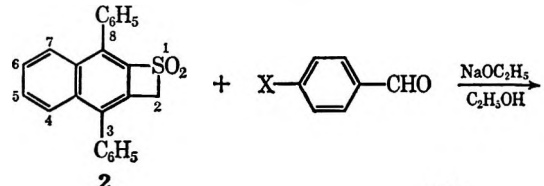
This investigation into the condensation reactions of aromatic aldehydes and cyclic, four-membered ring sulfones was undertaken to prepare derivatives of thietane sulfone with unsaturation exocyclic to the ring. We hoped that such sulfones might be reduced to the corresponding unsaturated sulfides, the reduction of the double bond or ring opening which occurs with thiete sulfones (where the olefinic bond is in the four-membered ring) being avoided.[6] Only 2,2-dimethyl-3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-dioxide and 2,2-dimethyl-3,10-diphenyl-2H-anthra-[3,2-*b*]thiete 1,1-dioxide are reduced cleanly to the sulfides and these thiete sulfones have no active methylene group.[6c]

Thietes are of theoretical interest because their anions are formally isoelectronic with the anion of cyclopentadiene. Reduction of the sulfone group in the 2-benzylidene derivative of 3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-dioxide might yield a thiete anion. Naphtho[8,1-*bc*]-thiete 1,1-dioxide (1)[7a] and some methylene thiete sulfones[7b] are the only known four-membered cyclic sulfones unsaturated at every position.

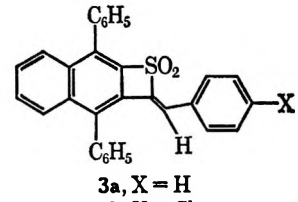


1

The naphthothiete sulfone **2**, when treated with benzaldehyde and sodium ethoxide in refluxing ethanol for 20 min, gave the unsaturated derivative **3a** in 96% yield. Similarly, *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde gave **3b** and **3c** (X = Cl, 77%; $-OCH_3$, 58%). No condensation reactions of this type with thiete sulfones are known; and the reaction is difficult with thietane sulfone, low yields of hydroxy compounds being obtained.[5b]



2



3a, X = H
b, X = Cl
c, X = OCH_3

All compounds had absorption in the infrared at 1300 and 1130–1145 cm^{-1} characteristic of the sulfone group.[1,6,6c] Absorptions caused by the olefinic group or by carbon–hydrogen bending vibrations of the olefinic group could not be assigned with assurance because of absorption by the aromatic rings. The proton nmr spectrum showed absorption at δ 6.20–6.33 (singlet) for a lone proton in addition to a multiplet for the aromatic protons.

The aryl group is probably *cis* to the sulfone group since models[8] indicate considerable steric interaction

(1) Paper II: D. C. Dittmer and F. A. Davis, *J. Org. Chem.*, **32**, 3872 (1967).

(2) This work was aided by National Science Foundation Grant GP 726 and by National Institutes of Health Grant CA 08250.

(3) Taken from the Ph.D. Thesis of J. M. Balquist, Syracuse University, Syracuse, N. Y., 1966.

(4) For recent determinations of pK_a values, see F. G. Bordwell, R. H. Imes, and E. C. Steiner, *J. Amer. Chem. Soc.*, **89**, 3905 (1967).

(5) (a) W. E. Truce and R. H. Knospe, *ibid.*, **77**, 5063 (1965); H.-D. Becker and G. A. Russell, *J. Org. Chem.*, **28**, 1896 (1963); G. A. Russell, H.-D. Becker, and J. Schoeb, *ibid.*, 3584; M. L. Oftedahl, J. W. Baker, and M. W. Dietrich, *ibid.*, **30**, 296 (1965). For condensations of Grignard reagents of sulfones, see L. Field and E. T. Boyd, *J. Org. Chem.*, **29**, 3273 (1964), and references cited therein. (b) For condensations with thietane sulfone, see S. M. Kotin, Ph.D. Thesis, University of Pennsylvania, Philadelphia, Pa., 1962.

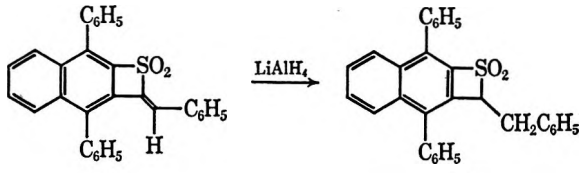
(6) (a) D. C. Dittmer and M. E. Christy, *J. Amer. Chem. Soc.*, **84**, 399 (1962); D. C. Dittmer and F. A. Davis, *J. Org. Chem.*, **29**, 3131 (1964); C. L. Schilling, M.S. Thesis, Syracuse University, Syracuse, N. Y., 1964. (b) D. C. Dittmer and N. Takashina, *Tetrahedron Lett.*, 3809 (1964). (c) L. A. Paquette, *J. Org. Chem.*, **30**, 629 (1965).

(7) (a) R. W. Hofmann and W. Sieber, *Angew. Chem. Intern. Ed. Engl.*, **4**, 786 (1965); *Ann. Chem.*, **703**, 96 (1967). (b) L. A. Paquette and M. H. Rosen, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p 14S.

(8) Framework Molecular Orbital Models, Prentice Hall, Inc.

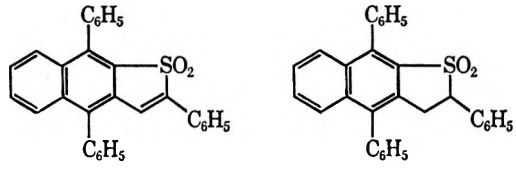
between the benzylidene phenyl group and the 3-phenyl group in a *trans* configuration.

Attempts were made to reduce the sulfone group of the benzylidene derivative **3a** by a tenfold excess of lithium aluminum hydride in tetrahydrofuran at −70° during 1–14 hr. The product recovery was 49–60% and consisted of a mixture of 13–32% of starting sulfone and 68–87% of 2-benzyl-3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-dioxide (**4**). The mixture was not able to be separated into its components. Elemental and mass spectrometric analyses of the product were consistent with its being a mixture of $C_{30}H_{20}O_2S$ (mol wt, 444) and $C_{30}H_{22}O_2S$ (mol wt, 446). The infrared spectrum of the product mixture is nearly identical with that of the starting unsaturated sulfone (**3a**) and of the sulfone **2**. The ultraviolet spectra of mixtures richer in **4** have greater absorption at 243, 313, and 343 mμ [ultraviolet spectrum of **2**: 241 (log ε 4.72), 315 (4.08), and 338 (3.96) mμ] which indicates saturation of the double bond; mixtures richer in **3a** have relatively greater absorption at 361 and 375 mμ.

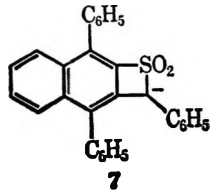


3a **4**

The mass spectrum of the mixture showed the most intense ion above *m/e* 100 at *m/e* 355 which corresponds to the loss of a benzyl group from **4**. The formation of $C_7H_7^+$ is inferred from an ion at *m/e* 91. The easy loss of a benzyl group supports structures **3a** and **4** over the alternate structures **5** and **6**. Further evidence against structure **5** is the observation that the sulfone group of alkyl-substituted benzthiophene sulfones is invariably reduced whereas the double bond may or may not be reduced.[9] The lack of reduction of the sulfone group of **4** may be caused by steric hindrance to attack on the sulfone or the sulfone anion (**7**); or its aluminohydride complex may be resistant to further attack by the reducing agent.



5 **6**



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(9) D. S. Rao, Abstracts, 137th National Meeting of the American Chemical Society, Cleveland, Ohio, April 1960, p 26O. See also F. G. Bordwell and W. H. McKellin, *J. Amer. Chem. Soc.*, **73**, 2251 (1951); G. Van Zyl, D. C. De Jongh, V. I. Heasley, and J. W. Van Dyke, *J. Org. Chem.*, **26**, 4946 (1961); G. Van Zyl and R. A. Koster, *ibid.*, **29**, 3558 (1963).

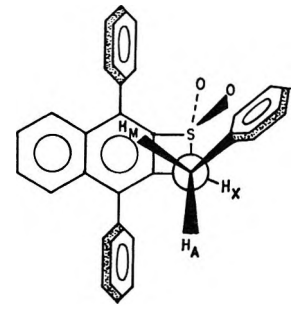


Figure 1.—Suggested preferred conformation of 2-benzyl-3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-dioxide.

From the proton nmr spectra the compositions of the mixtures from reduction can be determined. When the spectrum of the starting unsaturated sulfone **3a** is subtracted from the spectrum of the mixture, the relative intensities of the remaining absorptions for **4** are 19:1:1:1. The absorptions consist of a multiplet at δ 8.32–6.87 (19 aromatic protons), a quartet at 5.82–5.47 (one proton), a quartet at 3.67–3.10 (one proton), and a quartet at 2.94–2.52 (one proton). The quartet at δ 5.82–5.47 can be assigned to the proton H_X in Figure 1 since the absorption of the methylene protons in the naphthothiete sulfone **2** occurs at δ 5.10.[6b,c] The other two quartets ($\Delta\delta_{AM} \sim 0.7$ ppm) can be explained by the nonequivalence of protons H_A and H_M with $J_{AM} = 15$ cps, $J_{AX} = 3$ cps, and $J_{MX} = 11$ cps. These protons H_A and H_M do not alter their chemical shifts even at 200°. Proton H_A is assigned to the absorption at higher field because it is over the plane of the 3-phenyl group.[10] Models[8] indicate restricted rotation about the bond connecting the benzyl group to the four-membered ring because of steric hindrance by the 3-phenyl group and the sulfone group. The spin–spin coupling constant between two vicinal protons is related to the dihedral angle φ between the protons.[11] If ϕ_{AX} is about 70–45° and ϕ_{MX} about 140–160°, which are reasonable values according to a model, J_{AX} is calculated, according to the equation of Williamson and Johnson,[11a] to be about 3–5 cps and J_{MX} about 10–14 cps in agreement with the observed values. These calculated values are uncorrected for effects caused by changes in hybridization, in electronegativity, in H–C–C bond angles and in bond distances.

The relatively large difference in chemical shift of the two diastereomeric methylene protons H_A and H_M has analogies in the relatively large differences between the absorptions of methylene protons in [2.2]-metacyclophane,[12] in a pleiadene derivative,[13] in certain asymmetric benzyl ethers,[14] and in N,N-dimethylbenzylamines in which there was no plane of molecular symmetry.[15] The coupling constant of 15

(10) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, Chapter 7.

(11) (a) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961); (b) A. A. Bothner-By, *Adv. Magnetic Resonance*, **1**, 195 (1965).

(12) D. J. Wilson, V. Boekelheide, and R. W. Griffin, Jr., *J. Amer. Chem. Soc.*, **82**, 6302 (1960).

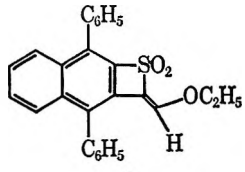
(13) P. T. Lansbury, *ibid.*, **81**, 4325 (1959).

(14) G. M. Whitesides, D. Holtz, and J. D. Roberts, *ibid.*, **86**, 2628 (1964); G. M. Whitesides, J. J. Grocki, D. Holtz, H. Steinberg, and J. D. Roberts, *ibid.*, **87**, 1058 (1935).

(15) J. C. Randall, J. J. McLeskey, III, P. Smith, and M. E. Hobbs, *ibid.*, **86**, 3229 (1964).

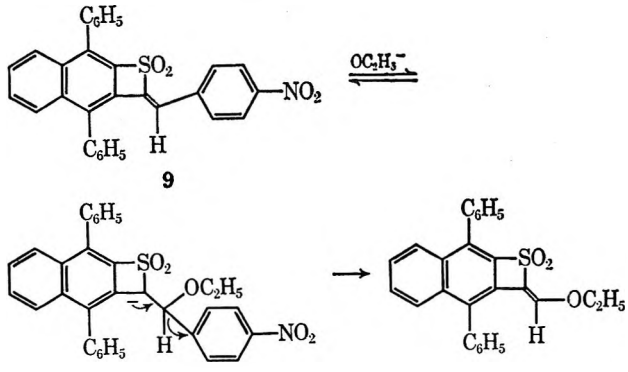
cps between H_A and H_M is in the range reported for geminal protons.[11b]

p-Nitrobenzaldehyde did not yield the *p*-nitrobenzylidene derivative but gave 8% of a light orange solid whose structure is suggested tentatively as **8** on the basis of its elemental analysis and infrared and ultraviolet spectra. The formation of **8** may proceed



8

by loss of the *p*-nitrophenyl group from the anion formed by addition of ethoxide ion to an intermediate benzylidene derivative, **9**. This reaction is somewhat



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analogous to the elimination of 1,3-dinitro-4,6-dimethoxybenzene from 2,6-dinitro-3,5-dimethoxybenzaldehyde when the latter is treated with 5% potassium hydroxide.[16]

Experimental Section[17]

2-(Benzylidene)-3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-Dioxide (3a).—To a refluxing solution of sodium ethoxide in ethanol, prepared by addition of 0.5 g (0.022 g-atom) of sodium to 100 ml of absolute ethanol, was added 1.78 g (0.005 mol) of 3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-dioxide (**2**)[6b,c] and 4 ml of benzaldehyde. The solution was refluxed for 15 min and cooled to room temperature. The precipitate was filtered, washed with cold absolute ethanol, and dried in a vacuum oven to give a light yellow powder (2.13 g, 96%, green-yellow fluorescence), mp 233–236°. Three recrystallizations from chloroform–ethanol produced an analytical sample, mp 240–241°.

Anal. Calcd for $C_{30}H_{20}O_2S$: C, 81.07; H, 4.54; S, 7.20; mol wt, 444. Found: C, 81.01; H, 4.60; S, 7.20; mol wt, 450 (osmometric).

The benzylidene sulfone had the following spectral properties: infrared (KBr) 3010 (w), 1600 (w), 1490 (w), 1440 (m), 1360 (m), 1300 (s), 1175 (s), 1130 (s), 790 (m), 770 (s), 695 (s) cm^{-1}; ultraviolet (CH_3CN), 219 mμ (log ε 4.03), 239 sh (3.85), 245 sh (3.83), 303 sh (4.18), 312 (4.22), 361 sh (3.85), 375 (3.86); nmr ($CDCl_3$), δ 8.38–7.18 (multiplet, 19 H), 6.34 (singlet, 1 H).

2-(*p*-Chlorobenzylidene)-3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-Dioxide (3b).—To a refluxing solution of sodium ethoxide in ethanol (prepared by dissolving 0.5 g (0.022 g-atom) of sodium in 50 ml of absolute ethanol) was added 1.44 g (0.004 mol) of 3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-dioxide followed by 4 ml of *p*-chlorobenzaldehyde. The solution was refluxed for 5 min, cooled to room temperature, and diluted with a 2:1 ethanol–water solution. The precipitate was collected by filtration, washed with cold ethanol, and dried in a vacuum oven to give a yellow solid (1.48 g, 77%) green-yellow fluorescence), mp 222–228°. Two recrystallizations from chloroform–ethanol produced an analytical sample, mp 236–238°.

Anal. Calcd for $C_{30}H_{19}ClO_2S$: C, 74.97; H, 3.99; Cl, 7.44; S, 6.67; mol wt, 478. Found: C, 75.25; H, 3.98; Cl, 7.30; S, 6.68; mol wt, 490 (osmometric), 478 (mass spectroscopy).

The *p*-chlorobenzylidene derivative had the following spectral properties: infrared (KBr) 3010 (w), 1590 (m), 1495 (m), 1300 (s), 1145 (s), 1095 (m), 840 (m), 770 (s), 700 (s) cm^{-1}; ultraviolet (CH_3CN), 223 mμ (log ε 4.17), 250 sh (4.00), 308 sh (4.29), 317 (4.33), 360 sh (4.00), 380 (4.07); nmr ($CDCl_3$), δ 8.28–7.03 (multiplet, 18 H) and 6.20 (singlet, 1 H); mass spectrum, *m/e* 478 (22%), 379 (24%), 378 (25%), 377 (20%), 376 (22%), 388 (29%), 337 (38%), 321 (24%), 310 (32%), 309 (38%), 302 (28%), 289 (22%), 262 (20%), 188 (23%), 187 (22%), 141 (39%), 139 (20%), 79 (25%), 78 (100%), 77 (92%), 76 (24%).

2-(*p*-Methoxybenzylidene)-3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-Dioxide (3c).—To a refluxing solution of sodium ethoxide in ethanol, prepared by dissolving 0.5 g (0.022 g-atom) of sodium in 70 ml of absolute ethanol, was added 1.0 g (0.0028 mol) of 3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-dioxide and 3 ml of redistilled *p*-anisaldehyde. The solution was refluxed for 1 hr, cooled to room temperature, diluted with 100 ml of saturated sodium chloride solution, and extracted with three 50-ml portions of chloroform. The organic layer was dried over anhydrous magnesium sulfate, concentrated to about 10 ml, and chromatographed on a Florisil column. The column was eluted with 1:1 benzene–chloroform. The eluent containing the first yellow band was collected and concentrated on a rotary evaporator by means of a water aspirator. Ethanol was added to precipitate a yellow powder (0.78 g, 58%, green-yellow fluorescence), mp 238–240°. Two recrystallizations from chloroform–ethanol produced an analytical sample, mp 245–247°.

Anal. Calcd for $C_{31}H_{22}O_3S$: C, 78.47; H, 4.67; S, 6.74; mol wt, 474. Found: C, 78.56; H, 4.93; S, 6.63; mol wt, 477 (osmometric), 474 (mass spectroscopy).

The *p*-methoxybenzylidene derivative had the following spectral properties: infrared (KBr), 3010 (w), 1600 (m), 1510 (m), 1300 (s), 1245 (s), 1175 (m), 1140 (s), 1020 (s), 860 (m), 770 (s), 760 (s), 695 (s) cm^{-1}; ultraviolet (CH_3CN), 223 mμ (log ε 4.53), 256 (4.44), 291 (4.39), 335 (4.66), 392 (4.44); nmr ($CDCl_3$), δ 8.28–7.30 (multiplet, 16 H), 7.02–6.72 (doublet, J = 9 cps., 2 H), 6.25 (singlet, 1 H), 3.77 (singlet, 3 H).

Partial Reduction of 2-(Benzylidene)-3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-Dioxide.—A solution of lithium aluminum hydride (1.90 g, 0.50 mol) in 200 ml of anhydrous tetrahydrofuran was cooled in a Dry Ice–acetone bath and the 2-benzylidene derivative (**3a**) (2.22 g, 0.005 mol) was added in powdered form. The solution was stirred 5 hr; then 20 ml of water in 100 ml of tetrahydrofuran was added slowly; and the solution was allowed to warm to room temperature. The solution was acidified with 5% hydrochloric acid solution, diluted with 300 ml of saturated sodium chloride solution, and extracted with three 200-ml portions of ether. The ether extract was dried over anhydrous magnesium sulfate, concentrated, and chromatographed on a Florisil column. The column was eluted with chloroform and the eluent containing the first yellow band was collected. The eluent was concentrated to *ca.* 3 ml and 40 ml of ethanol was added. The light yellow precipitate which formed was collected by filtration and dried in a vacuum oven to give 1.04 g (47% based on the weight of the recovered material) of a yellow solid, mp 186–194°, which was shown by proton nmr measurements to be a mixture of 13% starting material and 87% 2-benzyl-3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-dioxide (**4**). Three recrystallizations of a sample from a similar reaction (shown to contain 32% compound **3a** and 68% compound **4**) from chloroform–ethanol produced a sample, mp 188–189°, which was analyzed. The nmr spectrum indicated the sample was still contaminated with unreduced starting material.

Anal. Calcd for $C_{30}H_{20}O_2S$: C, 81.07; H, 4.54; S, 7.20; mol wt, 444. Calcd for $C_{30}H_{22}O_2S$: C, 80.70; H, 4.97; S, 7.17; mol wt, 446. Found: C, 80.90; H, 4.73; S, 7.08; mol wt, 450 (osmometric).

This mixture had the following spectral properties: infrared (KBr), 3010 (w), 2900 (w), 1590 (w), 1485 (m), 1435 (m),

(16) G. Lock and G. Nottes, *Monatsh.*, **68**, 51 (1936).

(17) Nmr spectra were recorded on a Varian A-60 spectrometer (60 Mc) and chemical shifts are reported with respect to tetramethylsilane. Infrared spectra were taken on a Perkin-Elmer Model 137 or 521 spectrophotometer. Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 spectrometer. Melting points are uncorrected and were obtained on a Fisher-Johns melting point block. Mass spectra were obtained on an Hitachi RMU-6D single-focusing mass spectrometer.

1360 (m), 1300 (vs), 1145 (vs), 775 (s), 755 (m), 700 (s) cm^{-1}; ultraviolet (CH_3CN), 219, 243 303 (sh), 313, 343, 358 (sh), and 375 mμ; nmr ($CDCl_3$), δ 8.32–6.88 (multiplet, relative area 19), 6.29 (singlet, relative area 0.13), 5.82–5.47 (quartet, relative area 0.87), 3.67–3.10 (quartet, relative area 0.87), and 2.94–2.52 (quartet, relative area 0.87); mass spectrum, *m/e* 446 (30%), 444 (42%), 412 (90%), 355 (100%), 262 (57%), 141 (37%), 105 (60%), 91 (18%) (base peak is at *m/e* 78 but *m/e* 355 was used as base for above).

Attempts at further reduction of **3a** by using a greater hydride to sulfone ratio or by using longer reaction times appear to lead to a complex mixture of undetermined nature.

Attempted Condensation of 3,8-Diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-Dioxide with *p*-Nitrobenzaldehyde.—To a refluxing solution of sodium ethoxide in ethanol, prepared by dissolving 0.5 g (0.022 g-atom) of sodium in 40 ml of absolute ethanol, was added 3,8-diphenyl-2H-naphtho[3,2-*b*]thiete 1,1-dioxide (1.78 g, 0.005 mol) followed by *p*-nitrobenzaldehyde (1.25 g, 0.008 mol). The solution was refluxed for 1 hr, cooled, diluted with 100 ml of saturated sodium chloride solution, and extracted with three 50-ml portions of chloroform. The organic layer was dried over magnesium sulfate, concentrated to about 10 ml, and chromatographed on a Florisil column. The column was eluted with 1:1 benzene–chloroform. The eluent containing the first orange band was collected and was concentrated on a rotary evaporator using a water aspirator. Ethanol was added to precipitate a light orange solid (0.18 g, 8%), mp 215–220°. Two recrystallizations from chloroform–ethanol produced an analytical sample, mp 227–228°, of a compound tentatively identified as 2-(ethoxymethylene)-3,8-diphenyl-2H-naphtho-[3,2-*b*]thiete 1,1-dioxide (**8**) which had the following spectral properties: infrared (KBr), 3000 (w), 1590 (m), 1500 (m), 1430 (m), 1325 (s), 1285 (vs), 1170 (s), 1120 (s), 950 (m), 850 (m), 825 (m), 770 (s), 695 (s), cm^{-1}; ultraviolet (CH_3CN), 218, 241, 316 (sh), 339, and 401 mμ. There was insufficient sample left for a proton nmr spectral analysis.

Anal. Calcd for $C_{26}H_{20}O_3S$: C, 75.79; H, 4.89; S, 7.78; mol wt, 412. Found: C, 75.82; H, 4.70; S, 7.62; mol wt, 416 (osmometric).

Further elution of the remaining column with chloroform produced 0.44 g of a red-orange solid which could not be recrystallized from chloroform–ethanol or from ethanol, but which precipitated from a concentrated chloroform solution on addition of an excess of petroleum ether (bp 65–75°). The red-orange solid from the second fraction had infrared and ultraviolet spectra similar to those of the previously obtained $C_{26}H_{20}O_3S$ compound. There was no characteristic aromatic nitro group absorption in the 1570–1500- and 1370–1330-cm^{-1} regions.

Registry No.—**3a**, 15856-32-3; **3b**, 15892-86-1; **3c**, 15856-33-4; **4**, 15814-50-3; **8**, 15814-51-4.

2-Oxazolidinones from an N-Dealkylation Reaction of Phosgene with Dialkylaminoalkanols. The Isolation and Reactivities of an N-Acyl Quaternary Ammonium Intermediate

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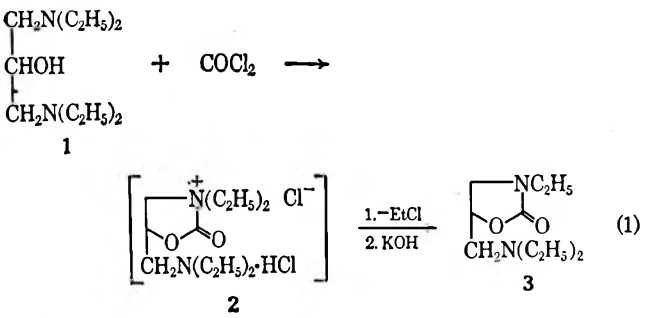
Received November 2, 1967

Phosgene condensed with 1-dimethylamino-2-propanol in the presence of pyridine to form a labile, cyclic N-acylium salt, **4**. This salt behaved as a powerful acylating agent toward *p*-toluenethiol, aniline, and methanol to form adducts **6**, **7**, and **8**. Toward chloride ion it was a mild methylating agent, concurrently forming 3,5-dimethyl-2-oxazolidinone **5**. Analogous formation of other oxazolidinones required a C substituent geminal to either the amino or hydroxyl group of the amino alcohol. A conformational explanation of this requirement for branching is proposed.

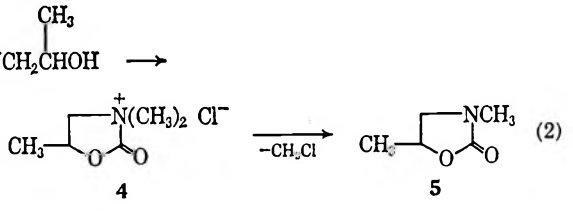
In another investigation phosgene was allowed to react with nonvicinal dialkylamino alcohols. Subsequent reaction of the unisolated condensation products with alcohols or nontertiary amines gave the expected carbonate esters or urethans,[1] but with bisdiethylamino alcohol **1** and phosgene the reaction took another course. With or without later addition of a secondary amine a cyclization–N-dealkylation reaction gave oxazolidinone **3**. By analogy with results described below it is probable that the cyclization proceeded *via* an N-acyl ammonium salt such as **2** (eq 1). Apparently one amino group served to bind hydrogen chloride, allowing acylation of the remaining free amino group.



(1) R. B. Angier, K. C. Murdock, and W. V. Curran, *J. Med. Chem.*, in press.

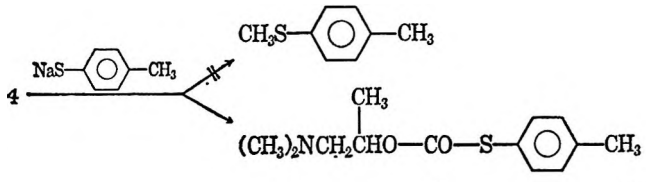
This report describes the isolation of a very reactive N-acyl ammonium analog of **2** and a study of its reactions with some representative nucleophiles. The scope of a novel synthesis of 2-oxazolidinones from phosgene and 2-dialkylaminoalkanols has also been explored.

When equimolar amounts of 1-dimethylamino-2-propanol and pyridine were added to excess phosgene in methylene chloride solution at $\leq -40°$, then allowed to come to room temperature, a crystalline solid separated. This solid gave analyses and an infrared absorption peak at 5.42 μ which were in accord (see below) with a cyclic N-acyl ammonium structure (**4**), but, when the crystalline acylium salt was allowed to remain at 25° in the stirred reaction mixture, it disappeared within 5 hr, forming 3,5-dimethyl-2-oxazolidinone (**5**) (see eq 2).



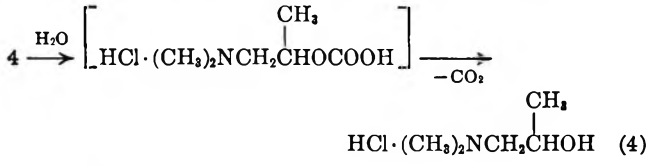
The same product was obtained instantly, along with gaseous methyl chloride, when the acylium salt was heated above its melting point (97°).

In contrast to the modest reactivity of **4** as an alkylating agent, it was found to be an avid acylating agent. In a competitive experiment with the sodium salt of *p*-toluenethiol in cold dimethylformamide solution no S-methylation was detected, while an S-acylation leading to **6** was very rapid (eq 3). Reaction with water gave



6 (3)

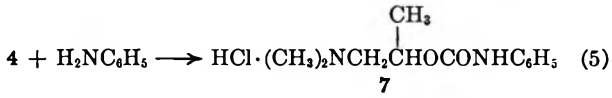
immediate effervescence, liberating carbon dioxide and the hydrochloride of the precursor amino alcohol (eq 4).



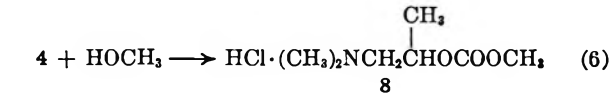
(4)

In fact, after 3 days in a stoppered vial a little "dry" **4** had all decomposed, also forming the same hydrochloride.

Acylation reactions in the cold with 1 equiv of aniline or methanol were complete within a minute or two, leading to urethan **7** and carbonate **8** in high yields (eq 5 and 6). The high reactivity of **4** as an



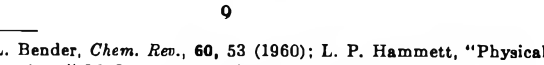
7 (5)



8 (6)

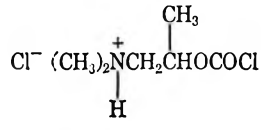
acylating agent is not unexpected. N-Acylium salts have long been postulated as intermediates in tertiary amine-catalyzed acylation reactions[2] of acid halides, anhydrides, and certain esters (and in N-dealkylation[3] reactions). Solid acylpyridinium salts of high lability and uncertain composition have been investigated by several groups.[4]

Klages and Zange characterized antimony pentachloride complexes with benzoyl chloride and trialkylamines, $C_6H_5CO\text{–}\overset{+}{N}R_2\ SbCl_6^-$, and demonstrated that they were powerful benzoylating agents.[5] Payne has reported the isolation of a well-defined adduct (**9**)



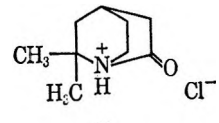
9

Spectral Correlations.—The infrared absorption maximum of acylium salt **4** at 5.42 μ and its high reactivity are in accord with the general association[7] of lowered wavelength of carbonyl absorption with heightened reactivity toward nucleophiles. In an open-chain model system we found that the position of the carbonyl peak of ethyl chloroformate in a cold methylene chloride solution was lowered from 5.63 to 5.49 μ after interaction with 1 equiv of triethylamine, presumably owing to formation of $C_2H_5OCO\overset{+}{N}(C_2H_5)_3\ Cl^-$. Conversely, when acylium salt **4** was allowed to stand for several days in methylene chloride saturated with hydrogen chloride the infrared absorption at 5.42 μ was almost entirely supplanted by a new peak at 5.64 μ, as might be expected for the formation of open-chain chloroformate structure **10**.



10

Another spectral model is the N-protonated form (**11**, ir peak at 5.56 μ) of the quinuclidone of Pracejus,[8] a compound in which the usual O protonation of amides is believed to be precluded by Bredt's rule. Thus, if the usual[9] 0.1-μ shift to lower wavelength is allowed for incorporation of a carbonyl group into a five-



11

membered ring, then a 5.42-μ peak would be reasonable for cyclic acylium salt **4** and would contraindicate a linear, polymeric N-acylium structure.

Oxazolidinone Syntheses.—When other β-dialkylamino alcohols were subjected to the conditions used in the above synthesis of oxazolidinone **5** it was found (Table I) that branching in the central carbon chain was essential for oxazolidinone formation. The results with 2,2-dimethyl-2-dimethylaminoethanol (**18**, in Table I) established, however, that the branching did not necessarily have to be at the hydroxylic carbon atom. This amino alcohol also gave an isolable, crystalline acylium salt intermediate (ir peak at 5.40 μ) analogous to **4**. Transient spectral peaks at 5.42 and 5.38 μ were also present in the reaction solutions from 1-diethylamino-2-propanol and *dl-erythro*-2-dimethylamino-1-phenyl-2-propanol (**17** and **19** in Table I). Without any branching the reaction took another course (eq 7). Thus the major product (52%) from

(2) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960); L. P. Hammett, "Physical Organic Chemistry" McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p 367; E. S. Gould, "Structure and Mechanism in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, pp 330–334.

(3) W. B. Wright, Jr., and H. J. Brabander, *J. Org. Chem.*, **26**, 4057 (1961), and references cited therein; F. Möller in Houben–Weyl's "Methoden der organischen Chemie," Vol. II, E. Müller, Ed., Thieme Verlag, Stuttgart, Germany, 1957, pp 985–987; R. F. Meyer and B. L. Cummings, *J. Heterocycl. Chem.*, **1**, 186 (1964); B. J. Calvert and J. D. Hobson, *J. Chem. Soc.*, 2723 (1965); A. C. Pierce and M. M. Joullié, *J. Org. Chem.*, **27**, 3968 (1962).

(4) F. Bayer and Co., German Patents 114,025, 117,625, 118,566; *Friedländer*, **6**, 1161, 1162, 1163 (1900). Chem. Fabrik von Heyden, A.-G., German Patents 109,933, 117,346, 116,386; *Friedländer*, **5**, 730, 954 (1900), and **6**, 1160 (1900). T. Hopkins, *J. Chem. Soc.*, **117**, 278 (1920). H. Adkins and Q. E. Thompson, *J. Amer. Chem. Soc.*, **71**, 2242 (1949). D. E. Koshland, Jr., *ibid.*, **74**, 2286 (1952).

(5) F. Klages and E. Zange, *Ann.*, **607**, 35 (1957).

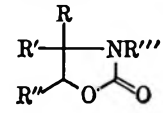
(6) G. B. Payne, *J. Org. Chem.*, **31**, 718 (1966).

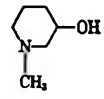
(7) H. A. Staab, *Angew. Chem. Intern. Ed. Engl.*, **1**, 351 (1961).

(8) H. Pracejus, *Chem. Ber.*, **92**, 988 (1959).

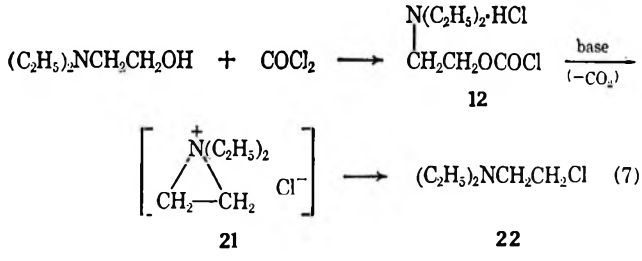
(9) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 42.

TABLE I
2-OXAZOLIDINONES FROM PHOSGENE AND 2-DIALKYLAMINOALKANOLS[a]



No.	Dialkylaminoalkanol	2-Oxazolidinone R	R′	R″	R‴	Yield, %	Formula	Calcd, % C	H	N	Found, % C	H	N
13	$(C_2H_5)_2NCH_2CHOH$		(compound 3)			68[b]	$C_{10}H_{20}N_2O_2$	60.0	10.1	14.0	60.0	10.1	13.9
14	$(CH_3)_2NCH_2CH_2OH$					0							
15	$(C_2H_5)_2NCH_2CH_2OH$					0							
16	$(CH_3)_2NCH_2\underset{CH_3}{\underset{\vert}{C}}HOH$	H	H	CH_3	CH_3	68[c]	$C_5H_9NO_2$	52.2	7.9	12.2	52.0	8.0	12.0
17	$(C_2H_5)_2NCH_2\underset{CH_3}{\underset{\vert}{C}}HOH$	H	H	CH_3	C_2H_5	77[d]	$C_6H_{11}NO_2$	55.8	8.6	10.8	56.1	8.8	10.7
18	$(CH_3)_2N\underset{CH_3}{\underset{\vert}{C}}H_2OH$	CH_3	CH_3	H	CH_3	80[e]	$C_6H_{11}NO_2$	55.8	8.6	10.8	55.9	8.9	10.9
19	$(CH_3)_2NCH\underset{CH_3}{\underset{\vert}{C}}HOH$[f]	H	CH_3	C_6H_5	CH_3	81[g]	$C_{11}H_{13}NO_2$	69.1	6.8	7.3	68.6	6.9	7.6
			(*dl-cis*)										
20						0							

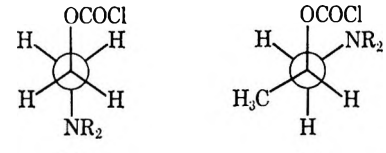
[a] The general synthetic procedure is described in detail in the Experimental Section for the preparation of **5**. [b] No pyridine was used in this synthesis: bp 104° (0.1 mm), $n^{26.7}$D 1.4610, λ_{max} 5.68 μ, neut equiv 188 and 185 (theory, 200.3). [c] Bp 63–65° (0.08 mm), $n^{25.0}$D 1.4470; A. B. Steele [U. S. Patent 2,868,801 (1959); *Chem. Abstr.*, **53**, 10261 (1959)] reports bp 92° (1.5 mm), n^{21}D 1.4464. [d] Bp 88° (1.2 mm), $n^{22.0}$D 1.4482; A. B. Steele[c] reports bp 87° (1 mm), $n^{21.2}$D 1.4458. [e] Bp 62° (0.05 mm), $n^{25.0}$D 1.4490. [f] Prepared by reaction of *dl*-norephedrine with formic acid and formaldehyde. [g] Mp 61–62° (from heptane); V. Ettel and J. Weichet [*Collect. Czech. Chem. Commun.*, **13**, 316 (1948); *Chem. Abstr.*, **42**, 8190 (1948)] report mp 57–58°.



12 **21** **22**

2-diethylaminoethanol and phosgene was 2-diethylaminoethyl chloride (**22**). (A little of the symmetrical carbonate ester of the amino alcohol was also obtained.) A chloroformate intermediate (**12**) could be isolated if reaction was brief and no added base was used.[10] Infrared spectral data did not reveal a reaction intermediate with a peak near 5.40 μ, and no 3-ethyl-2-oxazolidinone was found in the product. Results with 2-dimethylaminoethanol were analogous, and vapor phase chromatography detected no formation of 3-methyl-2-oxazolidinone. Participation of a neighboring amino group to form an ethylenimmonium intermediate (*i.e.*, **21**) is well precedented[11] and would explain the distinctive[12] lability of chloroformate **12** in the presence of base.

The decisive influence of branching may be explained by considering the probable conformations of chloroformate intermediates. Without branching, *anti* form **23** would predominate and be well disposed for a backside attack to generate an ethylenimmonium ion such as **21**. Moreover, resistance to formation of the ethylenimmonium ring system with its necessarily eclipsed substituents would be least when the carbon atoms of the ring bore only hydrogen atoms, but branching at either of the central carbon atoms would not only correspond to increasingly unfavorable eclipsing interactions in an ethylenimmonium pathway, but would generally favor *gauche* forms such as **24**, facilitating conversion into N-acylium salts (*i.e.*, **4**).



23 **24**

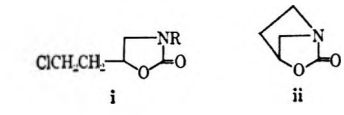
An attempt to form a bridged-ring oxazolidinone from 1-methyl-3-piperidinol (**20**, in Table I) was unsuccessful, as was an analogous attempt with a 1-methyl-4-piperidinol.[13] A low yield of a tetrahydro-

(10) A purer product might be obtained from the reported preparation of **12** from the hydrochloride of diethylaminoethanol: T. K. Brotherton, U. S. Patent 3,003,978; *Chem. Abstr.*, **57**, 5807 (1962).

(11) W. C. J. Ross, "Biological Alkylating Agents," Butterworth and Co., Ltd., London, 1962. B. Capon, *Quart. Rev.* (London), **18**, 62 (1964); S. D. Ross, *J. Amer. Chem. Soc.*, **69**, 2982 (1947); A. Streitweiser, "Solvolytic Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 105.

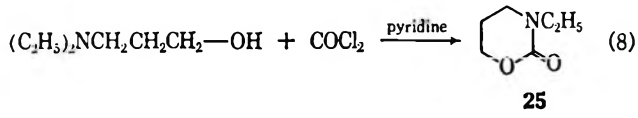
(12) Chloroformates are commonly purified by distillation without decomposing; elimination of carbon dioxide to form alkyl halides or olefins usually occurs only at higher temperatures: M. Matzner, R. P. Kurkjy, and R. J. Cotter, *Chem. Rev.*, **64**, 645, 670 (1964); K. W. Buck and A. B. Foster, *J. Chem. Soc.*, 2217 (1963).

(13) Earlier lack of success in attempts to synthesize the same bridged-ring oxazolidinones from 3- and 4-piperidinol by another method was believed to be due to lack of resonant stabilization of the amide link at the bridgehead N-atom of the desired product, as predicted by Bredt's rule [H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **80**, 6412 (1958)]. In this connection it seems pertinent that the tertiary amine promoted reaction of phosgene with N-alkyl-3-pyrrolicinols gave ring opening rather than loss of the N-alkyl group, *i.e.*, i rather than ii [M. L. Fielden, W. J. Welstead, and C. D. Lunsford, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y. Sept 1966, p 5P].



i ii

oxazinone (25, 2%) was obtained from 3-diethylamino-1-propanol (eq 8), but not from 3-dimethylamino-

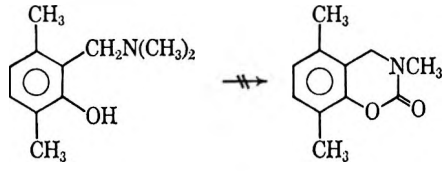


(8)

25

1-propanol or a branched-chain homolog, 4-dimethylamino-2-butanol.

Although *o*-(aminomethyl)phenol 26 might be expected to have special conformational restraints favoring cyclization, the product was apparently polymeric.



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Thus for practical purposes the present cyclization–dealkylation reaction appears to be limited to the synthesis of 3,4- and/or 5-substituted 2-oxazolidinones. Since many dialkylamino alcohols are more readily available than their monoalkyl- or N-unsubstituted analogs, this reaction conveniently supplements the previously reported routes[14] to 2-oxazolidinones.

Experimental Section

Evaporations were conducted under reduced pressure using a water aspirator. Solids were pressed with potassium bromide for infrared spectral determinations, liquids were scanned neat as smears. In monitoring the course of a reaction, *ca.* 0.01 ml of the reaction mixture was evaporated on 0.2 g of potassium bromide and the spectrum was obtained immediately with a Perkin-Elmer Infracord spectrophotometer. This procedure was effective even with liquid products. Other spectra were obtained with a Perkin-Elmer Model 21 spectrophotometer by W. Fulmor and his group. Microanalyses and gas chromatography were done by L. Brancone and C. Pidacks and their groups, respectively. Unless specified otherwise, liquid products were fractionated in a 42 cm × 0.8 cm Nester-Faust spinning-brush distillation column operated at 1125 rpm and having a rated maximum efficiency of about 58 theoretical plates.

3,3,5-Trimethyl-2-oxooxazolidinium Chloride (4).—To 200 ml of a 2 *N* solution of phosgene in methylene chloride kept at $\leq -40°$ was added dropwise with stirring a solution of 20.63 g (0.2 mol) of 1-dimethylamino-2-propanol and 15.82 g (0.2 mol) of dry pyridine in 200 ml of methylene chloride. The cooling bath was removed and stirring continued until (*ca.* 2 hr) the temperature had reached 20°. A 10-ml aliquot of the resulting suspension was removed. The solid therein was collected by filtration and washed with methylene chloride to yield 0.52 g: mp 96–97°, with gassing; λ_{max} 5.42, 8.45, 8.36 μ. [In an otherwise identical experiment all of the solid was collected giving 28.33 g (86%).] Analyses were done immediately.

Anal. Calcd for $C_6H_{12}NO_2Cl$: C, 43.5; H, 7.3; N, 8.5; Cl, 21.4. Found: C, 43.0; H, 7.9; N, 8.6; Cl, 21.5.

After 3 days in a capped vial the product no longer showed an infrared absorption peak at 5.42 μ; the spectrum was identical with that of the hydrochloride of the starting amino alcohol, except for a weak additional peak at 7.24 μ. Accordingly, all reactions of 4 were run with freshly prepared material.

3,3,4,4-Tetramethyl-2-oxooxazolidinium Chloride.—Starting with 23.44 g (0.2 mol) of dimethylamino-2-methyl-1-propanol the reaction was otherwise as in the preceding experiment. After 1.5 hr the temperature was 19°. The white solid in a 2.0-ml aliquot was collected by filtration to yield 0.121 g: mp 95–97°, with gassing; λ_{max} 5.40, 8.70, 8.53, 7.81 μ. Analyses were done immediately.

Anal. Calcd for $C_7H_{14}NO_2Cl$: C, 46.8; H, 7.9. Found: C, 47.0; H, 8.0.

3,5-Dimethyl-2-oxazolidinone (5).—The following general procedure was used to prepare the products of Table I. The main reaction mixture described for the preparation of acylium salt 4 (isolated from an aliquot) was stirred at 25° for an additional 5 hr, when an infrared spectrum no longer showed any of the 5.42-μ peak of 4. No additional spectral change was noted after another 15 hr. Solvent was removed by evaporation at $\leq 40°$, residual slush was agitated with 200 ml of dry ether, and solids were removed by filtration and washed with ether. Evaporation of the filtrate left a yellow oil which was distilled rapidly at 55–69° (0.07 mm), then fractionated, giving 15.25 g (68%) of distillate, λ_{max} 5.70 and 7.92 μ. Without the preliminary distillation the boiling point gradually dropped 7° during total reflux, after careful removal of forerun, indicating that a labile by-product in the still pot was gradually "cracking" to give volatile material.

Thermal Decomposition of 3,3,5-Trimethyl-2-oxooxazolidinium Chloride (4).—A test tube containing 0.166 g of 4 was fitted with a cork bearing a glass exit tube, then heated with an oil bath at 110–115° until (4 min) gas evolution stopped. The effluent gas gave an infrared spectrum which corresponded to the spectra[15] of methyl chloride and carbon dioxide. The residue was agitated with ether and the ether was filtered. Evaporation of the filtrate, finally at 0.05 mm, left 0.081 g (70%) of a colorless oil, $n^{26.2}D$ 1.4471. An infrared absorption spectrum from this oil was identical with that from 3,5-dimethyl-2-oxazolidinone (5), $n^{25.0}D$ 1.4470.

Carbonic Acid, Thiol-, O-2-Dimethylamino-1-methylethyl S-*p*-Tolyl Ester, Hydrochloride (6).—Two portions of petroleum ether were used to wash the oil (by decantation) from 0.439 g (0.01 mol) of a 54.7% suspension of sodium hydride in mineral oil. After the addition of 15 ml of dry dimethylformamide and 1.24 g (0.01 mol of *p*-toluenethiol to the finely divided sodium hydride, the mixture was agitated until gas evolution ceased. The solution was chilled and 1.65 g (0.01 mol) of 4 was added. The ice bath was removed. After 5 min an evaporated aliquot of the reaction mixture gave an infrared spectrum with no trace of the 5.42-μ peak of 4. Spectra obtained similarly after 1 and 20 hr showed no further change. The mixture was diluted with 45 ml of water and extracted with three portions of ether. The ethereal extracts were shaken successively with water, with 0.2 *N* sodium hydroxide solution, with water, with 1 *N* hydrochloric acid, and with water and then dried over anhydrous magnesium sulfate. Evaporation of the filtered ethereal solution left 0.272 g of a yellow oil with an infrared spectrum lacking the 6.62- and 12.46-μ peaks which were the most prominent peaks in the spectrum of methyl *p*-tolyl sulfide. After vapor phase chromatography of the oil, the fraction with a retention time corresponding to that of the sulfide still lacked these spectral peaks.

The acidic extract and the subsequent aqueous washes were evaporated, finally at *ca.* 0.1 mm, then dried further by evaporation with three successive portions of absolute ethanol. The residue was 2.06 g (71%) of a crystalline solid (mp 135–137° dec) or 1.7 g (mp 136–138° dec) after recrystallization from butanone.

Anal. Calcd for $C_{13}H_{19}NO_2S \cdot HCl$: C, 53.9; H, 6.9; N, 4.8; S, 11.1; Cl, 12.2. Found: C, 53.7; H, 7.0; N, 4.6; S, 10.7; Cl, 12.7.

Reaction of 4 with Water.—To 3 ml of water, magnetically stirred and chilled with an ice bath, was added 0.20 g of 4. An immediate effervescence was complete within a few seconds. The effluent gas gave an infrared spectrum identical with the spectrum[15] of carbon dioxide. A 0.04-ml aliquot of the reaction solution was evaporated at 0.1 mm on 0.2 g of potassium bromide (over phosphorous pentoxide) which was then pressed into a disk. The disk gave a sharp infrared spectrum identical with that obtained from the hydrochloride of 1-dimethylamino-2-propanol.

Reaction of 4 with Aniline. 2-Dimethylamino-1-methylethyl Carbanilate Hydrochloride (7).—A suspension of 8.28 g (0.05 mole) of 4 in 50 ml of methylene chloride was stirred at 5–10° during the dropwise addition of 4.22 g (0.045 mol) of aniline in 9 ml of methylene chloride. All of the suspended solid dissolved within 1 to 2 min and another solid began to separate almost immediately. An infrared spectrum obtained immediately from

(14) M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197 (1967).

(15) R. H. Pierson, A. N. Fletcher, and E. S. C. Gantz, *Anal. Chem.*, **28**, 1218 (1956).

an evaporated aliquot of this suspension showed none of the 5.42-μ peak of **4**. After 5 hr without further cooling, the mixture gave an infrared spectrum showing essentially no further change. The solution was diluted with ether to incipient turbidity. After several hours the resulting solid was collected by filtration and washed with methylene chloride–ether, 2:1, to give 10.22 g (87%) of glistening crystals (mp 146–149°) or 9.68 g (mp 147–149°) after crystallization from methylene chloride–ether, 2:1.

Anal. Calcd for $C_{12}H_{18}N_2O_2 \cdot HCl$: C, 55.7; H, 7.4; N, 10.8; Cl, 13.7. Found: C, 55.8; H, 7.5; N, 10.8; Cl, 14.1.

Reaction of 4 with Methanol. 1-Dimethylamino-2-propyl Methyl Carbonate Hydrochloride (8).—When the preceding experiment was repeated using 2.0 ml (1.6 g, 0.02 mol) of methanol instead of the aniline solution the observed responses of the two systems were very similar. The suspension was evaporated almost to dryness and washed once with cold methylene chloride. The resulting hygroscopic solid (6.98 g, mp 159–160° dec) was augmented by another 1.11 g (total 82%, mp 159–160°), obtained from the concentrated mother liquor.

Anal. Calcd for $C_7H_{15}NO_3 \cdot HCl$: C, 42.6; H, 8.2; N, 7.1; Cl, 18.0. Found: C, 42.4; H, 8.2; N, 6.9; Cl, 17.7.

Reaction of Phosgene with 2-Diethylaminoethanol. A. Hydrochloride of 2-Diethylaminoethyl Chloroformate.[12]—To 10 ml of a 2 *M* solution of phosgene in methylene chloride agitated at $\lesssim -40°$ was gradually added a dried, freshly distilled solution of 1.17 g (0.11 mol) of 2-diethylaminoethanol in 5 ml of methylene chloride. The resulting solution was immediately warmed to 24°, allowed to stand just 5 min, and then evaporated to dryness at $\lesssim 25°$, leaving 2.10 g (97%) of white solid: mp 208–212°; λ_{max} 5.64, 8.59 μ.

Anal. Calcd for $C_7H_{14}ClNO_2 \cdot HCl$: C, 38.9; H, 7.0; N, 6.5; Cl, 32.8. Found: C, 40.3; H, 7.5; N, 7.2, 7.0; Cl, 34.0, 34.2.

When a reaction solution was prepared as above and then allowed to stand at 25° for 16 hr, the indicated spectral peaks gradually became very much weaker.

B. 2-Diethylaminoethyl Chloride (22) and 2-Diethylaminoethyl Carbonate.—To 100 ml of a 2 *M* solution of phosgene in methylene chloride agitated at $\lesssim -40°$ was added at a fast drip a solution of 11.72 g (0.1 mol) of 2-diethylaminoethanol in 50 ml of methylene chloride. After 24 hr without further cooling the solution was evaporated to dryness. A chilled solution of the residual solid in 10 ml of water was carefully basified by the portionwise addition of 22.4 g of potassium hydroxide. The resulting thick slurry was extracted with three 40-ml portions of ether, readily separating the extracts by decanting from a round-bottomed flask. The extracts were dried over anhydrous potassium carbonate, filtered, and evaporated. Fractional distillation of the residue gave 7.06 g (52%) of a mobile oil [bp 64° (40 mm), $n^{23.3}D$ 1.4352] with an infrared spectrum identical with that from an authentic sample of 2-diethylaminoethyl chloride ($n^{23.2}D$ 1.4352).

Continued fractionation gave 0.38 g (3%) of a more viscous oil: bp 84° (0.05 mm); $n^{22.3}D$ 1.4422; λ_{max} 5.71, 7.95 μ [lit.[16] bp 112–116° (0.25 mm)].

Anal. Calcd for $C_{13}H_{28}N_2O_3$: C, 60.0; H, 10.8; N, 10.8. Found: C, 59.7; H, 10.8; N, 10.9.

When 0.79 g of 2-diethylaminoethanol was subjected to conditions used in the synthesis of **4** and **5** an infrared spectrum revealed no trace of an intermediate with a peak near 5.40 μ. The eventual neutral product was 0.034 g of an oil with an infrared spectrum which did not resemble the spectrum of 3-ethyl-2-oxazolidinone.[17]

Reaction of Phosgene with 2-Dimethylaminoethanol.—The reaction procedure paralleled that described for the synthesis of **4** and **5**, but no reaction intermediate with an infrared peak near 5.40 μ was detected. A comparative study with vapor phase chromatography and authentic 3-methyl-2-oxazolidinone revealed none of this compound in the scanty amount of crude, neutral product.

3-Ethyltetrahydro-2H-1,3-oxazin-3-one (25).—To 200 ml of a well-stirred, 2 *M* solution of phosgene in methylene chloride kept at $\lesssim -40°$ was added at a fast drip a solution of 26.94 g (0.2 mol) of 3-diethylamino-1-propanol and 15.82 g of dry pyridine in 200 ml of methylene chloride. After 4 hr without further cooling the initially most prominant spectral peak in the carbonyl region (at 5.52 μ) had disappeared and a peak at 5.93 μ had become dominant. The mixture was evaporated to dryness and the solid residue was washed with ether. Evaporation of the washes left 3.55 g of a mobile oil which was fractionally distilled twice without complete removal of a slightly lower boiling contaminant: bp *ca.* 78° (0.2 mm); $n^{25.3}D \gtrsim 1.4764$; λ_{max} 5.75 μ. Distillate cuts rich in this contaminant had a sharp odor and gave an especially heavy and immediate white precipitate with a solution of silver nitrate in nitric acid, suggesting the presence of a carbamoyl chloride. The contaminant was selectively destroyed by stirring most of the remainder of the better distillate cuts (1.21 g) for 22 hr with 5 ml of concentrated aqueous ammonia. The mixture was evaporated to dryness and the residual oily solid was washed with ether by decantation. Evaporation of the ether and simple distillation of the residual oil gave 0.58 g (2.3%) of an oil: bp 84° (0.1 mm); $n^{26.5}D$ 1.4690; λ_{max} 5.92 μ.

Anal. Calcd for $C_6H_{11}NO_2$: C, 55.8; H, 8.6; N, 10.8. Found: C, 55.6; H, 9.0; N, 11.0.

Registry No.—**3,** 15833-08-6; **4,** 15833-09-7; **5,** 15833-10-0; **6,** 15833-11-1; **7,** 15856-40-3; **8,** 15833-12-2; **17,** 15833-16-6; **18,** 15833-17-7; **19,** 15833-15-5; **25,** 15833-14-4; 3,3,4,4-tetramethyl-2-oxooxazolidinium chloride, 15833-13-3; hydrochloride of 2-diethylaminoethyl chloroformate, 15893-01-3; phosgene, 754-45.

(16) C. A. Dornfield, U. S. Patent 2,691,017; *Chem. Abstr.*, **49**, 15954 (1955).

(17) A. H. Homeyer, U. S. Patent 2,399,188; *ibid.*, **40**, 4085 (1946).

Synthesis of 4-Phenyl-1H-2,3-benzoxazine. A Convenient Route to a Rare Class of Compounds[1]

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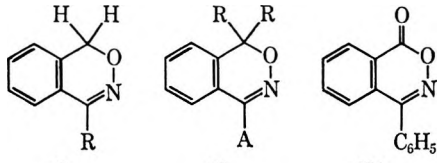
4-Phenyl-1H-2,3-benzoxazine, which is the first example of this type of compound having no substituent at the 1 position, was synthesized in four convenient steps from N,N-dimethylbenzylamine and benzonitrile. The final step, which involves cyclization of the lithio salt of a methiodide oxime, is presumably made possible by isomerization of the *cis* oxime salt to its *trans* isomer. The method should be applicable to ring-substituted N,N-dimethylbenzylamines and other aryl nitriles. An attempt to prepare the unsubstituted parent compound, 1H-2,3-benzoxazine, was unsuccessful.

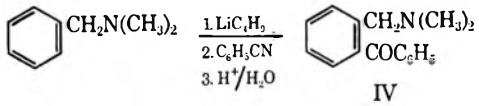
1,2-Oxazines in general are not well known in the literature,[2] and no benzoxazine of type I, which has no substituent at the 1 position, appears to have been described previously. Moreover, only one substituted benzoxazine of type I has been reported; the preparation of this compound, II (R, A = C_6H_5), involved treatment of the keto compound III with phenyl-



I II III

magnesium bromide and cyclization of the resulting carbinol oxime with hydrochloric and acetic acids.[3] Also, the "oxime" of phenolphthalein has been suggested to have structure II (R = 4-hydroxyphenyl, A = hydroxyl).[4]

Since ketoamine IV is readily available from N,N-dimethylbenzylamine and benzonitrile,[5] it seemed possible to prepare the benzoxazine I (R = C_6H_5) by oximation of the ketone group and methylation of the amine group of IV, followed by a base-catalyzed cyclization. This was realized in the present investigation.

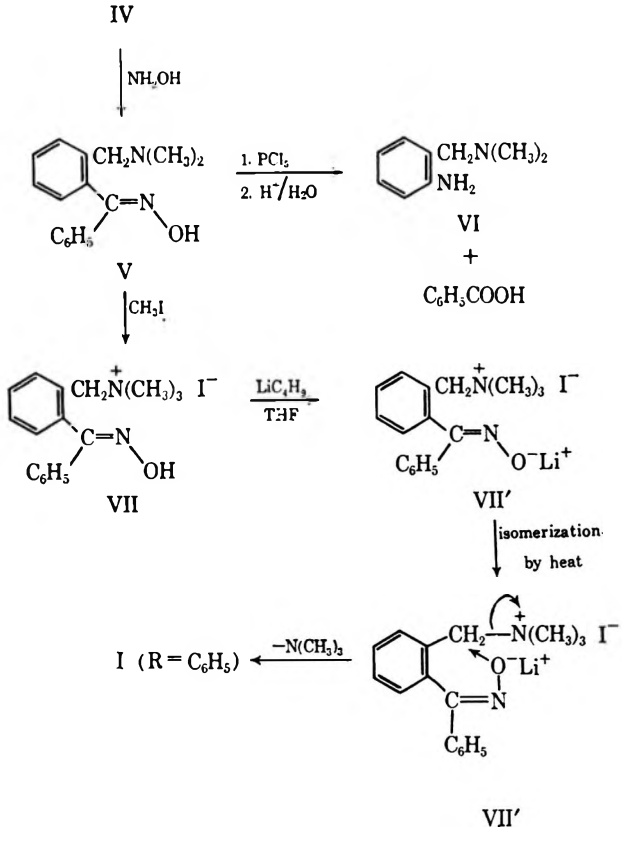


IV

The method of preparation of the benzoxazine I (R = C_6H_5) from ketoamine IV, and the establishment of the structure of the intermediate oxime through a Beckmann rearrangement, are indicated in Scheme I.

The intermediate oxime evidently has structure V since Beckmann rearrangement with phosphorous pentachloride afforded an amide, which yielded N^{α},N^{α}-dimethyltoluene-α,2-diamine (VI) and benzoic acid on hydrolysis.[6] The methiodide oxime VII, obtained as the sole methylation product, presumably had the same configuration, in which the hydroxyl and phenyl groups

SCHEME I



are *cis*. Since these groups must be *trans* in order for cyclization to occur, the *cis*-lithio salt VII′ apparently isomerized to the *trans*-lithio salt VII″ which underwent cyclization to give the benzoxazine I (R = C_6H_5). The yields from the oximation of ketoamine IV and the methylation of the resulting oxime V were excellent, and that from the cyclization was good; the over-all yield (based on IV) of I (R = C_6H_5) was 56%.

It can readily be seen that the method of preparation of I (R = C_6H_5) should provide a convenient route to several other new 1H-2,3-benzoxazines by employment of appropriately substituted N,N-dimethylbenzylamines and/or of other aryl nitriles. The method may also be suitable for the preparation of certain alkyl derivatives of I.

It should be mentioned that an attempt to prepare the methiodide oxime VII by reaction of the methiodide of ketoamine IV with hydroxylamine was unsuccessful; only starting material was recovered. Similarly, this methiodide was found to be unreactive toward phenylhydrazine. This failure can probably be ascribed to a steric factor.

(1) Supported by Public Health Service Research Grant No. CA-04455 from the National Cancer Institute.

(2) See R. L. McKee in "The Chemistry of Heterocyclic Compounds," Vol. 17, A. Weissberger, Ed., "Five- and Six-Membered Compounds with Nitrogen and Oxygen (Excluding Oxazoles)," R. H. Wiley, Ed., Interscience Publishers, Inc., 1962, Chapter 13.

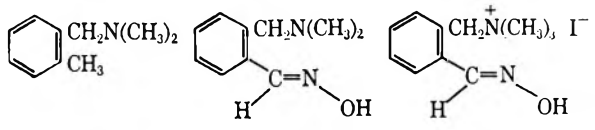
(3) A. Mustafa, W. Asker, M. Kamel, A. F. A. Shalaby, and A. E. A. E. Hassan, *J. Amer. Chem. Soc.*, **77**, 1612 1955).

(4) H. Lund, *Acta Chem. Scand.*, **8**, 1307 (1954).

(5) F. N. Jones, R. L. Vaulx, and C. R. Hauser, *J. Org. Chem.*, **28**, 3461 (1963).

(6) L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, **11**, 54 (1960).

Next, an attempt was made to prepare the benzoxazine I (R = H) by cyclization of the methiodide oxime X; the latter was prepared by methylation of the amino oxime IX which, in turn, was obtained by lithiation of amine VIII with *n*-butyllithium and treatment of the resulting lithioamine with *n*-butyl nitrite. However, treatment of the methiodide oxime X with *n*-butyllithium in tetrahydrofuran (THF) followed by heating (conditions used with VII) resulted in a substantial recovery of X together with trace amounts of other materials (probably arising by decomposition of the lithio salt of X). When the higher boiling solvent di-*n*-butyl ether was used, even more intractable materials were obtained.



VIII IX X

Experimental Section

All infrared spectra were measured as mulls in Nujol and hexachlorobutadiene unless otherwise stated, using a Perkin-Elmer spectrophotometer (Model 137). The ^1H nmr spectra were measured using a Varian A-60 spectrometer with tetramethylsilane as internal standard. Microanalyses were carried out by Jannsen Pharmaceutica, Beerse, Belgium, and also by M-H-W Laboratories, Garden City, Mich. Melting points were recorded on a Thomas–Hoover capillary melting point apparatus and are uncorrected.

Preparation of 2-(Dimethylaminomethyl)benzophenone (IV).—This was effected by using N,N-dimethylbenzylamine, *n*-butyllithium,[7] and benzonitrile, essentially as described previously.[5] Product IV recrystallized from hexane (charcoal) as large colorless prisms: mp 46–47° (lit.[5] mp 45–46°); ν_{max} 1660 (C=O), 1445, 1307, 1268, 1245, 928, 763, 737, 702 cm^{-1}.

Reaction of IV with Hydroxylamine to Form V.—A solution of hydrated sodium acetate (23.2 g, 0.17 mol) in water (50 ml) was added to a warm solution of IV (34.0 g, 0.14 mol) and hydroxylamine hydrochloride (11.9 g, 0.17 mol) in 95% ethanol (150 ml); the resulting solution was then boiled under reflux for 4 hr, cooled, and poured into stirred water (500 ml). The aqueous solution was neutralized with sodium bicarbonate and extracted with three 200-ml portions of ether. The dried ($MgSO_4$) ether solution was evaporated to provide a creamish solid (33.10 g, 92%) which, on crystallization from acetonitrile, provided the pure oxime (27.93 g, 77%) as colorless prisms: mp 126–128°; ν_{max} 2775 broad (OH), 1440, 1000, 934, 854, 770, 734, 695, 689 cm^{-1}; nmr ($CDCl_3$), τ −0.38 (broad singlet, hydroxyl), 2.14–3.02 (multiplet, aromatic), 6.64 (singlet, methylene), 7.86 (singlet, methyl), area ratio 1:9:2:6.

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.78; H, 7.16; N, 10.82.

Beckmann Rearrangement of V.—Phosphorous pentachloride (6.24 g, 0.03 mol) was added to a stirred solution of the finely divided oxime (5.08 g, 0.02 mol) in dry ether (200 ml) at 0°, to give a white suspension. The suspension was allowed to warm to room temperature during 0.5 hr and then stirred for a further 3 hr; during this time a clear solution which contained a greenish gum was obtained. The mixture was then poured, with stirring, into ice and water (300 g) to provide a clear solution. The colorless ether layer was separated, dried ($MgSO_4$), and evaporated, but no solid was obtained. The pale green aqueous layer was neutralized ($NaHCO_3$) when a yellowish oil separated and was extracted with ether (200 ml, then 100 ml). Evaporation of the dried ($MgSO_4$) ether solution afforded a viscous yellow oil (2.54 g) which could not be induced to crystallize. A further quantity of the oil (0.36 g) was obtained by concentration of the aqueous layer to *ca.* 60 ml and extraction with ether (100 ml, then 50 ml) as before. The total yield of the product was thus 2.90 g (57%). The infrared spectrum (liquid film) was consistent with that expected for a N-aryl-substituted benzamide, *e.g.*, ν_{max} 3200 (NH), 1660 (C=O).

The oil (2.40 g) was dissolved in 65% sulfuric acid (30 ml) and the solution was boiled under reflux for 2 hr; during this time benzoic acid vaporized and solidified in the condenser and was thus washed back into the solution with hot water (30 ml). When chilled overnight, the solution deposited a pale gray solid (0.49 g, 43%) which, on recrystallization from water, furnished benzoic acid (0.35 g, 30%) as colorless leaves, mp 121.5–122°.

The pale yellow filtrate was basified (cooling) with 10% sodium hydroxide solution and extracted with two 50-ml portions of ether. Evaporation of the dried ($MgSO_4$) ether solution yielded a brownish orange oil (0.47 g) which crystallized when chilled. The brown color was removed by pressing the solid between filter papers, leaving N^{α},N^{α}-dimethyltoluene-α,2-diamine (0.20 g, 14%) as colorless needles: mp 37–37.5° (lit.[8] mp 36–37°); ν_{max} 3445 (NH), 3310 (NH), 1615 (NH), 1495, 1455, 1285, 1020, 751 cm^{-1}.

Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65. Found: C, 71.48; H, 9.27; N, 18.25.

Reaction of V with Methyl Iodide.—Methyl iodide (12.42 g, 0.087 mol) was added during 4 min to a stirred suspension of V (18.5 g, 0.073 mol) in absolute ethanol (200 ml). After being stirred for a further 6 min at room temperatue, the suspension was boiled under reflux for 20 min when V dissolved. The cooled solution was poured, with stirring, into ether (700 ml) and the resulting white precipitate was collected and dried. Product VII (26.13 g, 91%) crystallized, with chilling, from acetonitrile to give the pure methiodide (23.89 g, 83%) as colorless acicular plates, mp 212–216° dec with darkening above 170°.

Anal. Calcd for $C_{17}H_{21}IN_2O$: C, 51.51; H, 5.30; I, 32.07; N, 7.07. Found: C, 51.72; H, 5.57; I, 32.38; N, 6.91.

Cyclization of VII to Give 4-Phenyl-1H-2,3-benzoxazine (I, R = C_6H_5).—A slight excess of a *ca.* 1.6 *M* solution of *n*-butyllithium in hexane (6.7 ml) was added dropwise over 5 min to a pale yellow suspension of VII (3.96 g, 0.01 mol) in dry THF (100 ml) at 0° under nitrogen; the suspension became colorless initially and then orange. After being stirred for a further 15 min at 0° without evolution of trimethylamine, the suspension was heated to reflux temperature during 30 min. Trimethylamine was now evolved and the reaction mixture was boiled under reflux until evolution of the gas had ceased (20 hr). During this time the color of the suspension became paler; after *ca.* 0.75 hr it was pale yellow, whereas after *ca.* 1.5 hr a green color developed.

The dark green suspension was filtered while hot to remove a small amount of a colorless (when washed with 10 ml of dry THF) solid which was largely water soluble and gave a positive test for iodide ion; this was presumably lithium iodide or recovered VII. Evaporation of the filtrate gave a dark green tar which could not be induced to solidify and was thus dissolved in the minimum volume of dry benzene and chromatographed on alumina (Fischer, 80–200 mesh). The colorless first fraction (which was sometimes eluted as a bluish green band) was eluted with a 1:1 mixture of petroleum ether (bp 30–60°) and benzene and then benzene, and, on evaporation, it afforded a dark green oil. This oil solidified on standing to provide a pale green solid (1.41 g, 67%) which, by two recrystallizations from hexane–benzene, furnished 4-phenyl-1H-2,3-benzoxazine (1.06 g, 51%) as clusters of colorless acicular plates: mp 76.5–77°; ν_{max} 1325, 1105 broad, 981, 860, 780, 760, 719, 696 cm^{-1}; nmr ($CDCl_3$), τ 2.17–3.00 (multiplet, aromatic), 5.05 (singlet, methylene), ratio 9:2.

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.61; H, 5.39; N, 6.59.

Evaporation of the other eluted fractions yielded small quantities of tarry materials together with lithium iodide; the latter was eluted with ethanol–methanol mixtures.

Attempted Reaction of the Methiodide of IV with Hydroxylamine.—A sample of ketoamine IV was treated with methyl iodide in absolute ethanol to form the methiodide: mp 175° dec with gradual darkening above 160° (lit.[5] mp 175° dec); ν_{max} 1670 (C=O), 1280, 1250, 934, 914, 894, 785, 777, 720 cm^{-1}.

To a warm solution of the methiodide (7.92 g, 0.02 mol) and hydroxylamine hydrochloride (1.30 g, 0.02 mol) in 95% ethanol (50 ml) was added a solution of hydrated sodium acetate (2.72 g, 0.02 mol) in water (10 ml). The resulting solution was boiled under reflux for 30 min, then allowed to cool. Filtration of the

(7) Used as supplied by Foote Mineral Co., Exton, Pa.

(8) E. Stedman, *J. Chem. Soc.*, 1902 (1927).

chilled reaction mixture furnished colorless crystals (1.89 g) and two more crops (total 5.13 g) were subsequently obtained from the filtrate. These crystals were identified as the starting methiodide of IV (65% recovery) by melting point and infrared spectrum.

Other reactions for longer periods or in the absence of hydrated sodium acetate gave similar results.

An attempted reaction between the methiodide of IV and phenylhydrazine in refluxing absolute ethanol which contained glacial acetic acid, resulted in an 88% recovery of the methiodide.

Reaction of *o*-N,N-Trimethylbenzylamine (VIII) with *n*-Butyllithium and *n*-Butyl Nitrite.—A slight excess of a *ca.* 1.6 *M* solution of *n*-butyllithium in hexane (267 ml) was added to a stirred solution of VIII[9] (59.6 g, 0.4 mol) in dry ether (100 ml) under nitrogen; after 2–3 hr, a cream-colored precipitate separated. The mixture was stirred at room temperature for 18 hr, during which time more dry ether was added to make up for losses by evaporation. The suspension was then added during 40 min to freshly prepared *n*-butyl nitrite[10] (20.6 g, 0.2 mol) at 0° to give an orange suspension initially which, toward the end of the addition, changed to a deep red solution; stirring at 0° was continued for a further 1 hr. The reaction mixture was poured into stirred water (200 ml) and the brown aqueous layer separated from the brown organic layer, acidified (glacial acetic acid), and neutralized ($NaHCO_3$). Extraction with three 200-ml portions of ether and evaporation of the dried ($MgSO_4$) ether layer furnished a viscous brown oil (10.64 g, 28%) whose infrared spectrum (liquid film) was consistent with that expected for the required oxime (IX): ν_{max} 3220 (OH), 2940 and 2850 (aliphatic CH), 1455, 1175, 1098, 1020, 965, 841, 758 cm^{-1}. This oil could not be induced to crystallize and was thus allowed to react with methyl iodide directly.

(9) W. R. Brasen and C. R. Hauser, *Org. Syn.*, **34**, 61 (1954).
(10) W. A. Noyes, *ibid.*, **16**, 7 (1936).

Reaction of the Crude Oxime (IX) with Methyl Iodide.—Methyl iodide (2.85 g, 0.020 mol) was added during 1 min to a stirred solution of the crude oxime IX (3.25 g, 0.018 mol) in absolute ethanol (30 ml) and, after *ca.* 50 min, a solid precipitated. The reaction mixture was stirred for a further 70 min and then filtered to give the crude methiodide (3.29 g); a further crop (0.52 g) was obtained by dilution of the filtrate with ether (400 ml); thus the total yield was 3.81 g (65%). Crystallization, with chilling, afforded the pure quaternary methiodide X (2.88 g, 49%) as colorless acicular plates: mp 196° dec with gradual darkening above 160°; ν_{max} 3240 (OH), 1477, 1407, 1370, 1285, 977, 961, 896, 888, 780, 763, 720 cm^{-1}.

Anal. Calcd for $C_{11}H_{17}IN_2O$: C, 41.26; H, 5.35; I, 39.64; N, 8.75. Found: C, 41.12; H, 5.44; I, 39.81; N, 8.60.

Attempted Cyclization of X.—A slight excess of a *ca.* 1.6 *M* solution of *n*-butyllithium in hexane (6.7 ml) was added during 5 min to a white suspension of X (3.20 g, 0.01 mol) in dry THF (100 ml) at 0° under nitrogen; the suspension became reddish brown and finally brown. Trimethylamine was evolved, and the solution was stirred at 0° for 15 min and allowed to warm to room temperature. After 16 hr trimethylamine was still being evolved; after making up the loss of solvent by evaporation, the suspension was boiled under reflux for 24 hr with the addition of more dry THF (50 ml) during this time. Although trimethylamine was still being evolved, the chocolate-colored suspension was allowed to cool and then filtered to provide a sticky brown solid (2.66 g) whose infrared spectrum showed it to be crude recovered X. Evaporation of the filtrate gave a reddish brown oil (1.25 g) which was chromatographed on alumina (Fischer, 80–200 mesh). Six different fractions were eluted, but each one yielded only an intractable tar on evaporation (total amount of tar, 0.75 g).

A second reaction, using di-*n*-butyl ether as solvent, gave similar results (probably owing to decomposition of the lithio salt of X).

Aminimides. VI.[1a,b] Synthesis of Aminimides from Carboxylic Acid Esters, Unsymmetrically Disubstituted Hydrazines, and Epoxides

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The reaction of unsymmetrically disubstituted hydrazines, epoxides, and carboxylic acid esters gives 1,1-disubstituted 1-(2-hydroxyalkyl- or aryl-)aminimides in excellent yields. Evidence is presented to support a primary reaction between the hydrazine and the epoxide to give an aminimine which subsequently reacts with the ester to give the aminimide. The aminimide may be pyrolyzed to give an isocyanate and a β-hydroxy tertiary amine which subsequently react to form a urethan.

Very little mention is made in the literature concerning the reaction between unsymmetrically substituted hydrazines and epoxides. In fact, only two references[2,3] could be found, both of which support the attack of the unsubstituted nitrogen on the terminal epoxide carbon atom (eq 1).

$$(CH_3)_2NNH_2 + RCH\text{—}CH_2 \longrightarrow \underset{\displaystyle OH}{\underset{|}{RCHCH_2NHN(CH_3)_2}} \quad (1)$$

1

It seemed more logical to us that the more nucleophilic substituted nitrogen would attack the epoxide to give the hydrazinium alkoxide 2 (eq 2). It is known from prior work[4] that alkoxides react with 1,1,1-trisubstituted hydrazinium salts to give aminimines. If 2 is formed, then it is logical to assume an extraction of a nitrogen proton by the alkoxide to provide the aminimine 3.

$$(CH_3)_2NNH_2 + RCH\text{—}CH_2 \longrightarrow \underset{\displaystyle O^-}{\underset{|}{RCHCH_2}}\overset{\displaystyle CH_3}{\overset{|}{\overset{+}{N}}}NH_2 \longrightarrow \underset{\displaystyle OH}{\underset{|}{RCHCH_2}}\overset{\displaystyle CH_3}{\overset{|}{\overset{+}{N}}}\overset{-}{N}H \quad (2)$$

CH_3 (2) CH_3 (3)

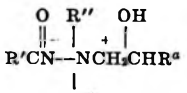
Results and Discussion

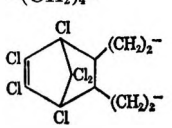
Since it was known[5,6] that aminimines react with carboxylic acid esters to produce aminimides, we tested

(1) (a) For paper V in this series, see B. M. Culbertson, E. A. Sedor, S. Dietz, and R. E. Fries, accepted for publication in *J. Polymer Sci., Part A-1*. (b) Presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968. (c) Current address is Calgon Corp., Calgon Center, Box 1346, Pittsburgh, Pa. 15230.
(2) F. Ya. Perveev and V. Ershova, *Zh. Obshch. Khim.*, **30**, 3554 (1960).
(3) G. Benoit, *Bull. Soc. Chim. Fr.*, **6**, 708 (1939).
(4) R. Appel, H. Heinen, and R. Schollhorn, *Chem. Ber.*, **99**, 3118 (1966).
(5) H. W. Schiessl and R. Appel, *J. Org. Chem.*, **31**, 3851 (1966).
(6) W. J. McKillip and R. C. Slagel, *Can. J. Chem.*, **45**, 2619 (1967).

Table I

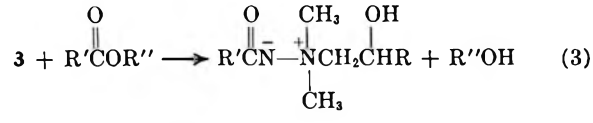
Properties of Aminimides and Data on Their Formation



Run no.	R′	R	Solvent, temp in °C	% yield	Mp, °C	TGA,[b] °C Onset	TGA,[b] °C Mid-point	Infrared absorption,[c] cm^{-1} O ‖ C—N	Infrared absorption,[c] cm^{-1} O—H	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
1	CH_3CH_2	CH_3	Isopropyl alcohol, 23	96	108.5–110	135	195	1600	3150	55.14	10.41	16.08	54.99	10.31	16.20
2	$CH_3(CH_2)_{10}$	CH_3	Isopropyl alcohol, 23	Quantitative	48–50	155	203	1570	3250	67.94	12.07	9.32	68.27	12.46	9.40
3	$CH_3(CH_2)_{10}$	$CH_3(CH_2)_5$	*t*-Butyl alcohol, 68	62	51.5–54.5	152	203	1570	3150	71.29	12.51	7.56	71.30	12.55	7.68
4	CF_3	CH_3	Isopropyl alcohol, 23	89	109–110	165	230	1650	3270	39.31	6.11	13.08	38.84	5.96	12.74
5	CF_3CF_2	CH_3	Isopropyl alcohol, 23	90.5	101–102	130	218	1660	3380	36.37	4.96	10.61	36.20	4.87	10.66
6	$CH_2{=}C(CH_3)$	CH_3	Isopropyl alcohol, 23	98	146.5–147.5	140	185	1580	3130	58.00	9.73	15.10	58.13	9.68	15.14
7	$CH_2{=}C(CH_3)$	H	*t*-Butyl alcohol, 23	88	78–80	139	188	1550	3120	55.78	9.36	16.26	56.05	9.18	16.25
8	$CH_2{=}C(CH_3)$	$CH_3(CH_2)_9$	Isopropyl alcohol, 23	Quantitative	64–66	155	187	1555	3225	69.17	11.61	8.96	69.30	11.51	9.07
9[a]	$CH_2{=}C(CH_3)$	CH_3	Isopropyl alcohol, 23	95	93–95	140	176	1555	3170	64.96	10.06	11.66	64.73	10.12	11.74
10	Ph	CH_3	*t*-Butyl alcohol, 23	94	122–125	168	211	1580	3125	64.84	8.16	12.61	65.20	8.11	12.71
11	Ph	Ph	*t*-Butyl alcohol, 23	90	146–147	162	195	1560	3090	71.80	7.09	9.85	71.89	7.12	9.81
12	Ph	*d*	*t*-Butyl alcohol, 55	55	182–183	175	208	1560	3180	68.66	8.45	10.74	68.42	8.22	10.81
13		CH_3	Isopropyl alcohol, 60	80	171 dec	...	...	1570	3150	68.53	10.06	9.99	68.38	10.05	9.83
14	$(EtO)_2P(O)(CH_2)_2$	CH_3	*t*-Butyl alcohol, 23	Quantitative	Oil	...	...	1600	3340	46.44	8.77	9.03	45.75	8.70	8.84
15		CH_3	Isopropyl alcohol, 23	Quantitative	116–118	175	225	1560	3325	59.17	7.68	18.82	59.38	7.62	18.85
16[e]	$-(CH_2)_4-$	CH_3	*t*-Butyl alcohol, 23	Quantitative	191–192	165	230	1570	3100	55.46	9.89	16.17	55.21	9.87	16.29
17[e]		CH_3	Isopropyl alcohol, 23	Quantitative	212 dec	205	277	1565	3100	42.80	5.62	8.68	42.50	5.64	8.65

[a] R′ ′= R‴ = CH_3 in all cases except run no. 9 where R″ = R‴ = $-(CH_2)_6-$. [b] Run on a Du Pont 950 thermogravimetric analyzer at 20°/min in nitrogen. [c] Run as mulls on a Perkin-Elmer 237B grating spectrophotometer. [d] Epoxide used was cyclohexene oxide. [e] The bisaminimides.

our hypothesis by allowing an unsymmetrically disubstituted hydrazine, an epoxide, and a carboxylic acid ester to react to see whether or not an aminimide (**4**) was produced (eq 3).

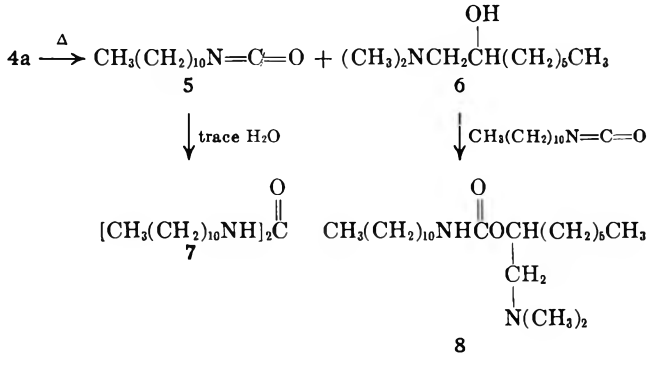


(3)

4a, R = $CH_3(CH_2)_5$; R′ = $CH_3(CH_2)_{10}$
b, R = CH_3; R′ = $CH_2{=}CCH_3$
c, R = H; R′ = $CH_2{=}CCH_3$
d, R = CH_3; R′ = CH_3CH_2
e, R = CH_3; R′ = CF_3CF_2
f, R = CH_3; R′ = C_6H_6

The first reaction studied was with unsymmetrical dimethylhydrazine, 1-octene oxide, and ethyl laurate in *t*-butyl alcohol. Heating the reactants together at 68° for 8 hr resulted in a 62% yield of a waxy product identified as 1,1-dimethyl-1-(2-hydroxyoctyl)amine-laurimide (**4a**). The structure was determined by infrared (O–H absorption at 3150 and typical aminimide absorption at 1570 cm^{-1} in halocarbon mull) and nmr (CCl_4, τ; N-methyl peaks at 6.58 ppm gave the expected integration) spectroscopy, elemental analysis, and the products of pyrolysis. Pyrolysis of **4a** gave the expected results,[7] *i.e.*, the β-hydroxy tertiary amine **6**, the symmetrical urea **7**, and the urethan **8** (Scheme I). The isocyanate **5** may be isolated if the hydroxy group of **4a** is converted into the acetate ester prior to pyrolysis.

SCHEME I



The Scope of the Reaction.—Further investigation showed that the scope of the reaction is very broad (Table I, p 1375). The ester may be aliphatic, fluorinated aliphatic, α,β-unsaturated, aromatic, or difunctional. The epoxide may be one of long- or short-chain α-olefins, of internal olefins, or of aromatically substituted olefins. The unsymmetrically disubstituted hydrazine may be an aliphatic substituted hydrazine such as 1,1-dimethylhydrazine or aminohexamethylenimine. It was found, however, that 1-methyl-1-phenylhydrazine did not react with propylene oxide, probably because of the reduced nucleophilicity of the nitrogen substituted by the phenyl group.

The effect of solvent on the reaction is shown in Table II. It is interesting to note that, with the exception of highly polar dimethyl sulfoxide, only the protonic solvents gave high yields of aminimide **4b**. Dimethyl sulfoxide, however, was shown to be an ineffective solvent in the *in situ* synthesis of aminimides from hydrazine halides, esters, and sodium methoxide.[6] The aminimide was formed in quantitative yield even if no solvent was used.

TABLE II
EFFECT OF SOLVENT[a] ON YIELD OF **4b**

Solvent	% yield
Benzene	9.6
t-Butyl alcohol	91.5
Dimethyl sulfoxide	88.0
Isopropyl alcohol	98.0
Methanol	97.0
Tetrahydrofuran	5.4
Water–ethyl alcohol	Quantitative
No solvent	Quantitative

[a] Reactions run at room temperature for 72 hr with 0.1 mol of each reactant in 50 ml of solvent.

Most of the reactions reported in Table I were run at room temperature for 16–48 hr with yields ranging from 88% to quantitative. In runs 3, 12, and 13, lower yields were obtained despite higher reaction temperatures. These lower yields are probably all attributable to a highly decreased rate of reaction due to steric hindrance at the reaction sites. Such is the case at least with the adamantane derivative (run 13) where the aminimide formed very slowly over a period of 22 hr even at 60°. Other less hindered aliphatic esters reacted much more readily.

An example of how the rate of reaction increases with temperature is shown in Table III. Aminimide **4b** forms readily at 80° in 2 hr or less, whereas at room temperature only a 50% yield is obtained after 2 hr.

TABLE III
EFFECT OF TEMPERATURE[a] ON YIELD OF **4b**

Temp, °C	% yield
Room temperature	50
40	76
60	91
80	95

[a] Two-hour reaction with 0.1 mol of reactants in 50 ml of isopropyl alcohol.

One would expect the reaction rates to increase with increasing electron-withdrawing ability of the group on the ester if the aminimine is the attacking species on the ester carbonyl.[5,6] This was found to be the case as shown from the rate data in Figure 1. At the initial stages of the reaction, it is apparent that the relative order of rates is CF_3CF_2— > $CH_2{=}CCH_3$ ≥ C_6H_5— > CH_3CH_2—.

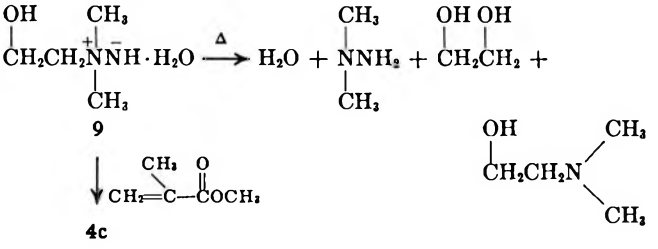
Mechanism.—The work just described suggests that the reaction probably proceeds through the intermediate aminimine (eq 2). To establish this, we tried the reaction in isopropyl alcohol with no ester present. After 4 days at room temperature, the solvent was evaporated *in vacuo* at room temperature to give a very hygroscopic, heat-sensitive, viscous oil whose analysis agreed with **3** (R = CH_3). Reaction of the oil with methyl methacrylate in isopropyl alcohol gave **4b** in near quantitative yield.

These results lead us to seriously question the earlier work by Perveev[2] and Benoit[3] which supports eq 1.

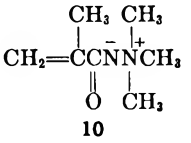
(7) W. J. McKillip, L. M. Clemens, and R. Haugland, *Can. J. Chem.*, **45**, 2613 (1967).

Benoit[3] carried out the reaction of 1,1-dimethylhydrazine and ethylene oxide in water. Conceding that the solvent might make some difference, we repeated Benoit's work. Evaporation of the water *in vacuo* at 40° or lower gave a very hygroscopic, white crystalline solid in quantitative yield. This material was identified as the monohydrate of **3** (R = H) or **9**, by infrared and nmr spectroscopy, elemental analysis, and, finally by its reaction with methyl methacrylate to give a quantitative yield of **4c**. Similar results were obtained using propylene oxide. Benoit[3] distilled his reaction product to obtain what he identified as **1** (R = H). Distillation of our product (**9**) (decomposition starts at 86°) proceeded to give the products shown in Scheme II with no trace of **1** (R = H) as a product. The products that we observed were not surprising since pyrolysis of hydrazinium hydroxides, which are probably the same as aminimine hydrates, have been shown to give similar products.[8] For example, 1,1,1-trimethylhydrazinium hydroxide was pyrolyzed to give water, 1,1-dimethylhydrazine, methyl alcohol, and trimethylamine all analogous to the products of Scheme II as well as nitrogen, ammonia, dimethylamine, and N,N,N′,N′-tetramethyldiaminomethane.[9] Our decomposition was carried out at reduced pressure, and we did not attempt to isolate any gaseous products.

SCHEME II



To provide further evidence that hydrazinium hydroxides are actually aminimine hydrates, we prepared 1,1,1-trimethylhydrazinium hydroxide in isopropyl[10] alcohol and added methyl methacrylate. Trimethylamine methacrylimide (**10**)[11] was obtained in high yield.



Consequently, our work has shown that the synthesis of aminimide from *unsym*-disubstituted hydrazines, epoxides, and esters follows the general pathway outlines in eq 1 and 2.

Structure of the Hydroxyaminimides.—Table I shows the infrared absorption of the carbonyl function in the aminimides to be at 1550–1660 cm^{-1}, depending on R′. As has been described previously,[12,13] the absorption is at too low a frequency for a typical acylhydrazinium-type carbonyl group and thus resonance form **11** must contribute to the over-all structure of the compound. The actual structure probably involves a distribution of the negative charge over the nitrogen, carbon, and oxygen atoms,[12] the degree depending mainly on R′.

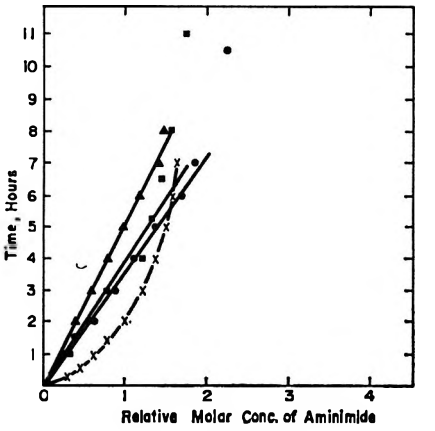
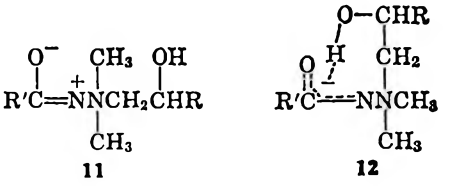


Figure 1.—The relative rates of formation of ●, **4b**, ▲, **4d**, × **4e**, and ■, **4f**.



It is interesting to note the exceptionally low frequency of the O–H stretch (Table I) indicating a strong hydrogen bond between the hydroxyl proton and the negative charge center, either inter- or intramolecular or both. The molecule is properly situated to form a *quasi* six- or eight-membered ring depending on whether the negative charge is closer to the nitrogen or oxygen atom. The infrared spectrum of **4b** in chloroform at three dilutions (1, 4.5, and 19%) showed a strong bonded O–H stretching at 3230 cm^{-1} with only a very weak free O–H stretch at 3655 cm^{-1}. This result indicates that the hydrogen bonding is mainly, if not entirely, intramolecular as in **12**.

Experimental Section[14]

General Synthesis of Aminimides in Table I.—A mixture of 0.1 equiv of each reactant (*i.e.*, ester, *unsym*-disubstituted hydrazine and epoxide) in 50–100 mol of the solvent indicated was allowed to stir at the temperature indicated for 16–48 hr, as was convenient. Exceptions include run 3 which was carried out at room temperature for 72 hr and then at 68° for 8 hr, run 12 at 55° for 48 hr, and run 13 at 60° for 22 hr. The preferred reaction vessel was a pressure bottle stirred magnetically, although a simple flask with an efficient condenser was also suitable. At the end of the reaction period, the solvent was removed *in vacuo* to give the crude yield. Most compounds were recrystallized two or three times from benzene or ethyl acetate to provide the analytical samples. The long-chain alkyl derivatives were recrystallized from hexane.

Pyrolysis of 1,1-Dimethyl-1-(2-hydroxyoctyl)aminelaurimide (4a).—Pyrolysis of 2.0 g of the aminimide was carried out in a Carius tube at 160° for 2 hr. Cooling provided a partially solid

(8) H. H. Sisler and G. M. Omietanski, *Chem. Rev.*, **57**, 1031, 1033 (1957).
(9) F. Klages, G. Nober, F. Kircher, and M. Bock, *Ann.*, **547**, 1 (1941).
(10) G. L. Braude and J. H. Cogliano, U. S. Patent 3,225,101 (1965).
(11) R. C. Slagel and A. E. Bloomquist, *Can. J. Chem.*, **45**, 2625 (1967).
(12) S. Wawzonek and E. Yeakey, *J. Amer. Chem. Soc.*, **82**, 5718 (1960).
(13) T. A. Sokolova, L. A. Ovsyannikova, and N. P. Zapevalova, *Zh. Org. Khim.*, **2**, 818 (1966).

(14) Melting points and boiling points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. The nmr spectra were obtained on a Varian A-60A spectrometer in the solvent indicated using tetramethylsilane as an internal standard except with deuterium oxide where 3-trimethylsilyl-1-propanesulfonic acid was used as the standard. Elemental analyses were performed by Huffman Laboratories, Inc., Wheatridge, Colo.

mass. The solid was filtered and washed with hexane to give 0.2 g of a white crystalline material, mp 103–105°. The infrared (3340, 1625, 1590 cm^{-1}) spectrum, elemental analysis, and melting point (lit.[15] mp 103°) show the structure to be symmetrical diundecylurea.

Anal. Calcd for $C_{23}H_{48}N_2O$: C, 74.93; H, 13.12; N, 7.60. Found: C, 74.43; H, 12.96; N, 7.46.

The filtrate was evaporated to give 1.8 g of a colorless liquid. Distillation gave 0.4 g of a colorless oil, bp 45° (0.35 mm), $n^{22}D$ 1.4367. This oil was identified as N,N-dimethyl-1-amino-2-octanol by comparing the boiling point, refractive index, and infrared spectrum with those of the known material made from 1-octene oxide and dimethylamine in isopropyl alcohol at room temperature.

The pot residue from the above distillation was filtered to give another 0.2 g of the urea. The remaining viscous oil showed infrared absorption bands at 3340 and 1725 cm^{-1}, among others, indicating the presence of urethane. We were unable to purify this material sufficiently to obtain a satisfactory elemental analysis. However, reaction of the known isocyanate with the known amino alcohol gave a product showing the same infrared spectrum.

Aminimide 4a was treated with an equimolar amount of acetic anhydride in benzene[16] to provide 1,1-dimethyl-1-(2-acetoxyoctyl)aminelaurimide, identified by the disappearance of the 3150-cm^{-1} absorption bands in the infrared spectrum and the appearance of a band at 1745 cm^{-1}. The acetate was pyrolyzed at 150° (0.05 mm) to give an oil which was immediately fractionally distilled to give a 39% yield of pure undecyl isocyanate, bp 77–84° (0.05 mm), identified by the boiling point [lit.[17] bp 103° (3 mm)], infrared spectrum (sharp band at 2270 cm^{-1} for a thin film), and conversion into symmetrical diundecylurea.

Reaction of 1-Methyl-1-phenylhydrazine, Propylene Oxide, and Methyl Methacrylate.—Equimolar (0.05 mol) amounts of the reactants were placed in 50 ml of isopropyl alcohol and sealed in a pressure bottle. The reaction was allowed to stir at room temperature for 16 hr. A sample was removed and evaporated to give only the starting hydrazine. The reaction was continued for 4 hr at 80° and for 1.5 hr on the steam bath with the same result.

Rate Study of Aminimide Formation.—Solutions were made up with 0.01 mol of distilled unsymmetrical dimethylhydrazine, propylene oxide, and the ester (methyl methacrylate, ethyl propionate, ethyl perfluoropropionate, and methyl benzoate) in 20 ml of isopropyl alcohol. The solutions were immediately transferred to a 0.1-mm liquid infrared cell. The reactions were run at 23 ± 1°. Formation of the corresponding aminimide was followed by the increasing intensity of the band at 1550–1675 cm^{-1}. Each reaction was allowed to continue for at least 7 hr with spectra recorded periodically.

Several concentrations were made of each authentic aminimide in isopropyl alcohol and plotted *vs.* the absorbance of the 1550–1675-cm^{-1} infrared band. The absorbance of the experimental runs described above was then related to the known concentration plot to give the results shown in Figure 1.

Synthesis of 3 (R = CH_3).—Freshly distilled unsymmetrical dimethylhydrazine (0.1 mol) and propylene oxide (0.1 mol) were dissolved in 60 ml of Spectral Grade isopropyl alcohol. A portion was sealed in a vial which remained at room temperature for 4 days. The solvent was evaporated *in vacuo* at room temperature over phosphorus pentoxide to give a very viscous hygroscopic oil. The analytical sample was transferred under dry nitrogen.

Anal.[18] Calcd for $C_5H_{14}N_2O$: C, 50.81; H, 11.94. Found: C, 51.32; H, 11.95.

The aminimine (0.05 mol) was again placed in 50 ml of isopropyl alcohol and 0.05 mol of methyl methacrylate was added. The resulting solution stirred at room temperature for 24 hr. A quantitative yield of the aminimide **4b** resulted in evaporation of the solvent (by melting point, mixture melting point, and infrared spectrum).

Synthesis of 9.—Freshly distilled unsymmetrical dimethylhydrazine (12.0 g, 0.2 mol) was dissolved in 100 ml of water and placed in a pressure bottle which was cooled with an ice bath. Ethylene oxide (4.4 g, 0.1 mol) was added and the bottle was then sealed. The reaction proceeded at ice bath temperature for 1 hr after which the bath warmed to room temperature and remained there for a total reaction time of 16 hr. The solvent was evaporated *in vacuo* at 40° to provide 13 g of a white crystalline solid. A sample of the solid was dried *in vacuo* at 23° over phosphorus pentoxide for 48 hr. The dried sample had mp 83° with decomposition at 86°. The infrared spectrum (halocarbon mull) showed absorption at 3400, 3240, 3120, 3030, 2820, 2700, 1650, and 1475 cm^{-1}, etc. The nmr spectrum (τ, D_2O) showed six protons at 6.63 (N-methyl protons) and four protons in a multiplet centered at 6.18 ppm.

Anal. Calcd for $C_4H_{14}N_2O_2$: C, 39.32; H, 11.55; N, 22.94. Found: C, 39.54; H, 11.27; N, 23.02.

The hydrate 9 (0.01 mol) was dissolved in 10 ml of isopropyl alcohol along with 0.01 mol of methyl methacrylate. The solution was stirred for 16 hr at room temperature. Evaporation of the solvent and drying the product *in vacuo* over phosphorus pentoxide gave a near-quantitative yield of **4b** as determined by melting point, mixture melting point, and the infrared spectrum.

Reaction of Unsymmetrical Dimethyl Hydrazine and Propylene Oxide in Water.—The above procedure was repeated except that equimolar amounts of the reactants were used. A quantitative yield of product was obtained. The dried sample had mp 83° with decomposition at 90°. The infrared spectrum (nujol mull) showed absorption at 3420, 3250, 3160, 3030, and 1660 cm^{-1}, etc. The nmr spectrum (τ, D_2O) showed a doublet at 8.83, two peaks at 6.52 and 6.58 (N-methyl protons), and a multiplet at 5.58 ppm in an expected area ratio of 3:6:1, respectively.

Anal. Calcd for $C_6H_{16}N_2O_2$: C, 44.09; H, 11.84; N, 20.57. Found: C, 44.53; H, 11.62; N, 20.11.

Reaction with methyl methacrylate, as above, gave a near-quantitative yield of **4b**.

Pyrolysis of 9.—The aminimine hydrate 9 (28 g) was pyrolyzed at 115° (30 mm). A colorless liquid distilled at 39–47° totalling 17.4 g. Redistillation of the liquid gave a first fraction containing water and unsymmetrical dimethylhydrazine, both identified by glpc (6-ft dimethylpolysiloxane on Chromosorb W column). Unsymmetrical dimethylhydrazine was also identified by comparing its methyl iodide salt with known 1,1,1-trimethylhydrazinium iodide (melting point, mixture melting point, and infrared spectrum). The second, and last, fraction had bp 125–128°, $n^{25}D$ 1.4274, and was shown to be N,N-dimethyl-1-amino-2-hydroxyethane by comparison of the infrared spectrum and the methyl iodide salt (mp 263°, mixture melting point not depressed) with those of the known material.

The pot residue from the pyrolysis contained starting material and ethylene glycol. The latter was identified by its infrared spectrum and glpc retention time.

Reaction of Trimethylhydrazinium Hydroxide with Methyl Methacrylate.—1,1,1-Trimethylhydrazinium chloride (5.5 g, 0.05 mol) was dissolved in 200 ml of isopropyl alcohol and then passed over a Dowex 1-X4 ion-exchange column (200 g of resin) in the hydroxyl form.[10] Excess methyl methacrylate was added to the effluent and the mixture was allowed to stir at room temperature overnight. Evaporation of the solvent gave a quantitative yield of **4b** identified by comparing the melting point, mixture melting point, and infrared spectrum with those of authentic **4b**.

Acknowledgment.—The author is grateful to Arnold E. Bloomquist for excellent technical assistance and to Drs. L. M. Clemens and E. A. Sedor for helpful discussions involving this work.

(15) C. Naegeli, L. Grüntuch, and P. Lendorff, *Helv. Chim. Acta*, **12**, 227 (1929).

(16) K. N. Campbell, C. J. O'Boyle, and B. K. Campbell, *Proc. Indiana Acad. Sci.*, **58**, 120 (1949); *Chem. Abstr.*, **44**, 4418*h* (1950).

(17) C. F. H. Allen and H. Bell, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 846.

(18) The Dumas nitrogen determination was not satisfactory. This is not surprising since the determination uses a carbon dioxide purge and it is known that aminimines react with carbon dioxide; see ref 4.

Mass Spectra of Some Di- and Triazaindenes

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The mass spectra of imidazo[1,2-*a*]pyridine (I), imidazo[1,5-*a*]pyridine (II), imidazo[1,2-*a*]pyrimidine (III), and various methyl derivatives are reported and analyzed. The parent compounds lose HCN and C_2H_2N. In the methyl derivatives, analogous fragmentations occur. In addition, the loss of a hydrogen atom from the methyl group results in possible ring-expanded products which subsequently lose HCN as well as C_4H_4. The major fragmentations of the parent ion radicals are in agreement with the ion-radical bond orders.

As part of our continuing studies of the chemistry of polyazaindenes,[1] we now wish to report and analyze the mass spectral cleavage patterns of some imidazo-[1,2-*a*]pyridines (I), imidazo[1,5-*a*]pyridines (II), and imidazo[1,2-*a*]pyrimidines (III).

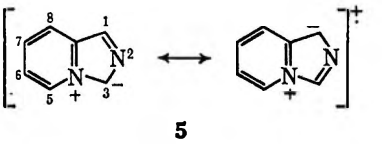
The major fragmentations of aromatic nitrogen heterocyclic systems that have been described to date can be outlined as shown in Chart I.

Thus, the loss of HCN (*m/e* 27) appears to be the major fragmentation path in pyridines,[2] quinolines,[3] naphthyridines,[4] quinoxalines,[4] quinazolines,[4] indoles,[2] and pyrazines.[2,5] The methyl derivatives of these heterocyclic systems either lose a hydrogen or a methyl radical to afford species **2** or **4**, respectively. Species **2**, a presumed ring-expanded ion, loses HCN when structurally possible.

The presence of a nitrogen atom at the bridgehead of the polyazaindenes, under study in our laboratories, represents a structural variation of considerable interest in terms of its influence upon the fragmentations of these compounds.

Scheme I outlines the paths which are common to the ring systems studied. The facile one-step loss of HCN (*m/e* 27) is typical of these compounds and is substantiated by metastable ions. The 3-methylimidazo-[1,5-*a*]pyridine loses CH_3CN to a much greater extent (Σ_{37} 8.9%) than it loses HCN (Σ_{37} 2.82%). Thus, bonds 1–2[6] and 3–4 are cleaved more readily than the 1–9 and 2–3 bonds.

The simultaneous cleavage of bonds 1–9 and 3–4 in these compounds to yield the species **6** or **6′** is confirmed by suitable metastable transitions. That we are in fact dealing with the cleavage of bonds 1–9 and 3–4, and not some other bonds, is shown by deuterium labeling. The *m/e* 78 peak in the 3-deuteroimidazo-[1,2-*a*]pyridine is not shifted to *m/e* 79. On the other hand the *m/e* 79 peak (**6**) in the 5-deuteroimidazo-[1,2-*a*]pyrimidine is, in fact, shifted to *m/e* 80. Similarly the 3-deuteroimidazo[1,5-*a*]pyrimidine affords the *m/e* 78 peak only and no *m/e* 79 peak.



5

The bond orders (Table I) calculated for the polyazaindenes described in the foregoing discussion are in agreement with the observed fragmentation patterns.

TABLE I

BOND ORDERS OF SOME POLYAZAINDENES

Compd	Bond order (p_{AB}) for bond AB: $p_{1,2}$ Ground state	$p_{1,2}$ Ion radical	$p_{2,3}$ Ground state	$p_{2,3}$ Ion radical	$p_{1,4}$ Ground state	$p_{1,4}$ Ion radical	$p_{1,9}$ Ground state	$p_{1,9}$ Ion radical
	0.644	0.753	0.632	0.487	0.474	0.484	0.495	0.463
	0.592	0.573	0.677	0.696	0.536	0.585	0.656	0.459
	0.673	0.819	0.527	0.272	0.486	0.507	0.468	0.365

The loss of HCN from the imidazo[1,2-*a*]pyridine (I) and from the imidazo[1,2-*a*]pyrimidine (III) might be predicted from the lengths of the 1–9 and 2–3 bonds in the ion radicals of these two compounds. These bonds possess much more single-bond character than the clearly doubly bonded atoms 1 and 2.

The cleavage of bonds 1–9 and 3–4 to afford the ion radical **6** (Scheme I) is also predicted by the length of the 3–4 bond (*cf.* Table I), which has a considerable amount of single-bond character.

In the case of the imidazo[1,5-*a*]pyridine (II), one can envision loss of HCN to occur by either cleavage of bonds 1–9 and 2–3 or by rupture of bonds 1–2 and 3–4. Since we have now shown that the latter process predominates, we would expect that the 2–3 bond possess much more double-bond character than the 1–2 bond. Table I clearly shows this to be the case.

(1) W. W. Paudler and L. S. Helmick, *Chem. Commun.*, 377 (1967); W. W. Paudler and J. E. Kuder, *J. Org. Chem.*, **32**, 2430 (1967).

(2) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra," Holden-Day, Inc., San Francisco, Calif., 1964, pp 225–258.

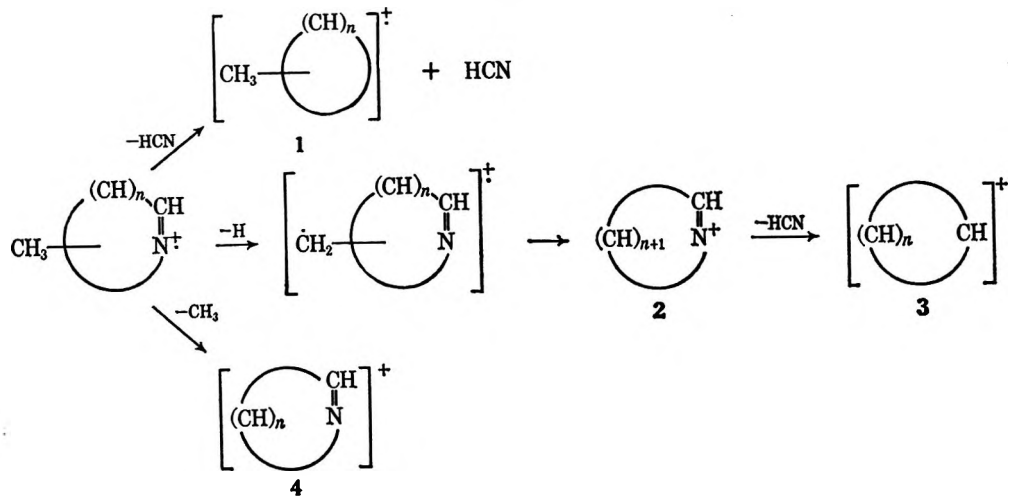
(3) S. D. Sample, D. A. Lightner, O. Buchart, and C. Djerassi, *J. Org. Chem.*, **32**, 997 (1967).

(4) W. W. Paudler and T. J. Kress, presented at the 1st International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 1967; *J. Heterocycl. Chem.*, **4**, 547 (1967).

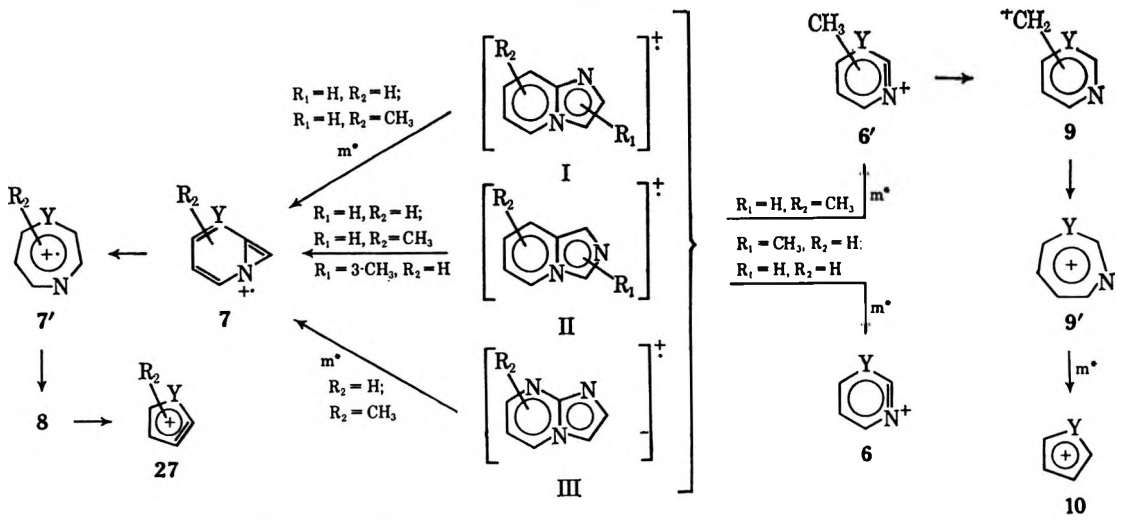
(5) A. L. Jenninga, Jr., and J. E. Boggs, *J. Org. Chem.*, **29**, 2065 (1964).

(6) For the sake of clarity in the discussion, all compounds are numbered as shown in structures **5**.

CHART I



SCHEME I[a]



[a] For structures I and II, Y = CH; for structure III, Y = N.

The fragment **7** loses HCN to yield the species **8**. This process can be envisioned to occur *via* the ring-expanded ion radical **7′**.

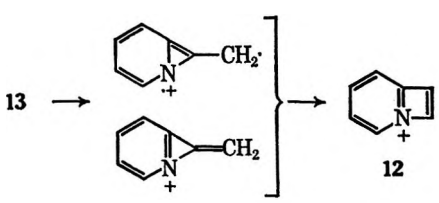
If such a ring expansion occurs, prior to HCN loss, we would anticipate the species **8** to appear with equal intensity at *m/e* 64 and 65 in the 3-deuteroimidazo-[1,2-*a*]pyridine. This has, in fact, been shown to be the case.

Ions **6** and **6′** fragment further by processes identical with those observed in the mass spectra of 2-halopyridines and of 2-halopyrimidines (loss of either CN or C_2H_2, etc.).

The ion **6′** can rearrange to **9′** prior to loss of HCN to form the ion **10**. The formation of **9′** is strongly supported by the fact that ion **6′** obtained from the 5-methyl compounds loses HCN to the same extent as all of the other monomethyl compounds with the methyl groups substituted in the six-membered ring. Also, the ratios of species **9** to **10** is essentially constant within a given series of compounds. Thus, the formation of the ring-expanded ion **9′** is strongly implied.

Fragmentations Typical of Methyl-Substituted Compounds. A. Methyl Groups Substituted on the Five-Membered Ring.—The generally most pronounced process typical of polyazaindenes substituted in the five-membered ring with a methyl group involves the loss of a hydrogen atom to form the species **11** (*cf.* Scheme II). These ions can ring expand to form the bicyclic systems represented by **11′**. The loss of HCN from these ions affords the species **12** (substantiated by a metastable transition). This ion fragments further by loss of C_2H_2 to afford the pyridyne ion **6**. Thus, this ion is formed by two different paths (*cf.* Scheme I also), both of which are substantiated by metastable ion peaks.

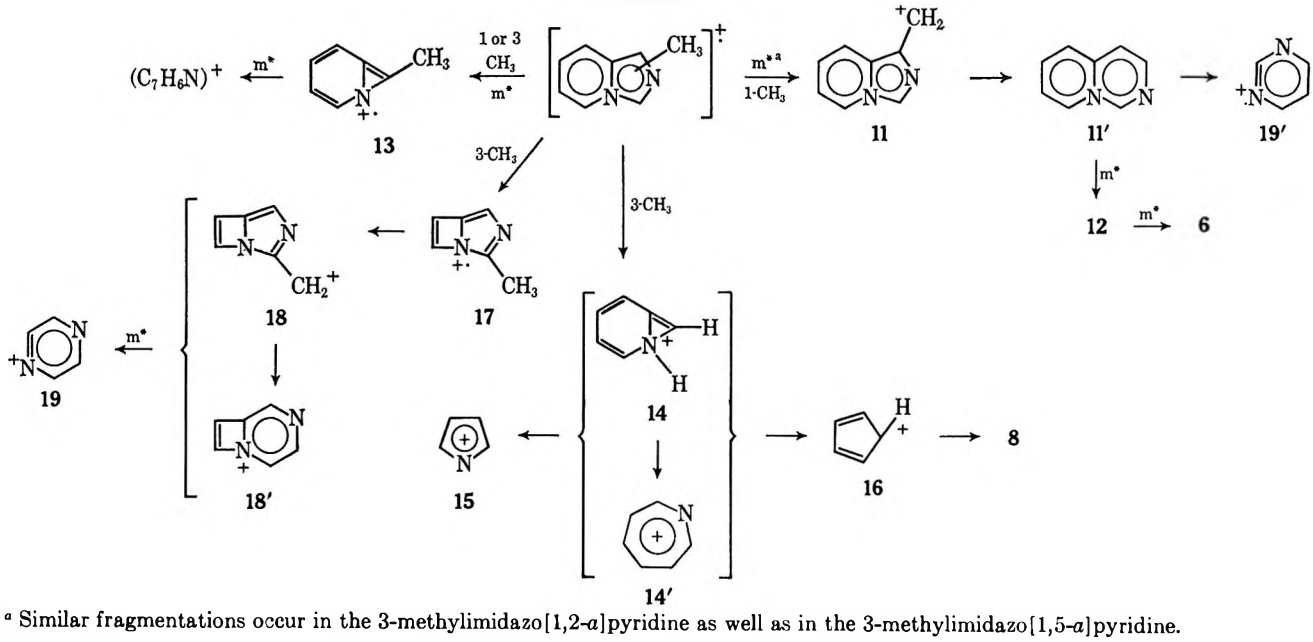
Depending upon the ring system, the loss of HCN, described in Scheme I, can also occur in these methyl derivatives. The ion radical **13** (*m/e* 105) is indeed observed in the cases studied (*cf.* Scheme II). This ion loses a hydrogen atom (supported by a metastable ion peak) to afford the species $(C_7H_6N)^+$. This may well have the structure **12**, if **13** undergoes the transformation in eq 1.



(1)

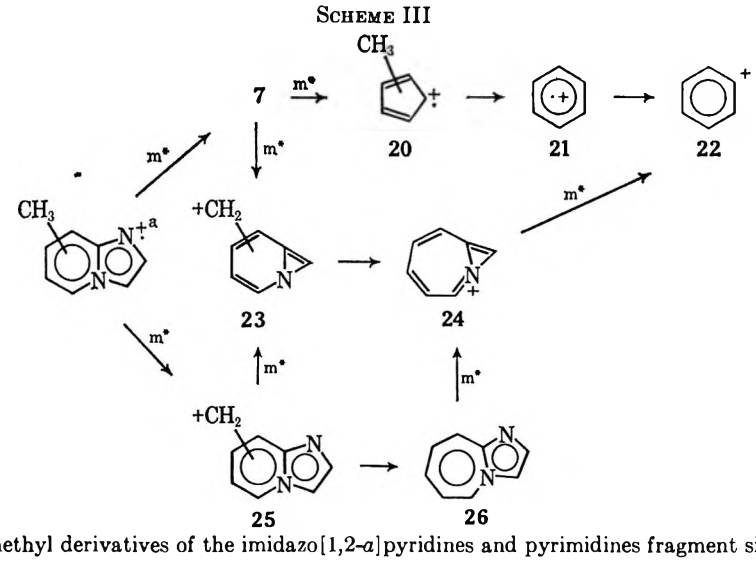
The *m/e* 105 ion radical **13** could, potentially, lose CH_3CN to afford a *m/e* 64 ion **8**. However, among the monomethyl compounds with the substituent in the

SCHEME II



[a] Similar fragmentations occur in the 3-methylimidazo[1,2-*a*]pyridine as well as in the 3-methylimidazo[1,5-*a*]pyridine.

SCHEME III



[a] The six-membered ring methyl derivatives of the imidazo[1,2-*a*]pyridines and pyrimidines fragment similarly.

five-membered ring, this species is only present in the mass spectrum of the 3-methylimidazo[1,5-*a*]pyridine. Consequently, it must arise from another path which is specific for this compound.

In fact, the 3-methylimidazo[1,5-*a*]pyridine undergoes two fragmentation paths which are not observed in the other methylpolyazaindenes described in this paper.

The formation of the *m/e* 92 ion **14** (or **14'**) must result from a hydrogen migration from the methyl group to either the bridgehead nitrogen atom or the carbon atom at position 5 (only the former alternative is shown in Scheme II). This species can ring expand to form the azatropylium ion **14'** which in turn can lose C_2H_2 and HCN to form the ions *m/e* 66 (**15**) and *m/e* 65 (**16**), respectively. The latter can stabilize itself somewhat by loss of a hydrogen atom to form the cyclopentadienyl ion radical **8**.

The second fragmentation path typical of the 3-methylimidazo[1,5-*a*]pyridine involves the loss of C_2H_2 from the parent ion radical to afford the bicyclic system **17** which in turn loses a hydrogen atom to afford **18**. This species may well ring expand to afford the ion **18'** which then loses C_2H_2 to afford the pyridyne ion **19**. The latter step is substantiated by the presence of a metastable transition.

B. Methyl Groups Substituted on the Six-Membered Ring.—During the discussion of the fragmentations described in Scheme I, we pointed out that the loss of HCN is the most pronounced process that occurs in these electron-impact reactions. The presence of methyl groups in the six-membered ring opens some additional avenues for fragmentation(s). Thus, ion **20** forms what we believe to be the ring-expanded ion radical **21**. This ion radical loses a hydrogen atom to form the species **22**. The loss of a hydrogen atom from **7** to afford the ion **23** is substantiated by a metastable transition. This ion can be envisioned to undergo a ring expansion to afford the bicyclic system **24**, which loses HCN to yield the ion **22**, Scheme III. This process is again substantiated by a metastable transition.

Species **25** results from loss of a hydrogen atom from the parent ion radical. This species then loses HCN to afford the ion **24** possibly *via* the ring-expanded

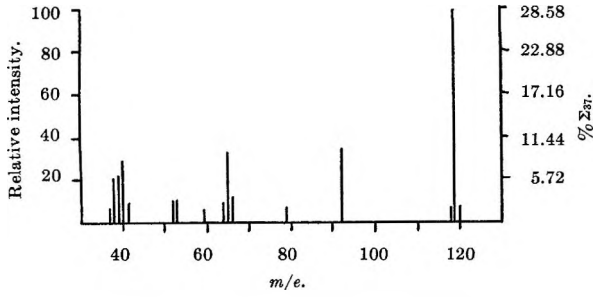


Figure 1.—Mass spectrum of imidazo[1,2-*a*]pyrimidine.

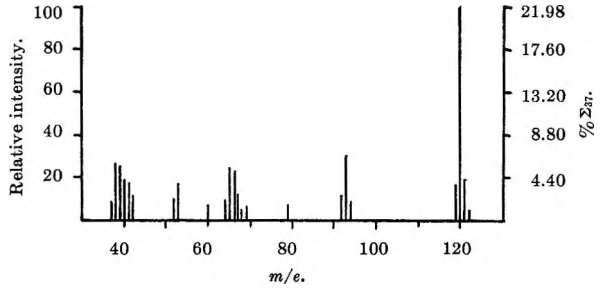


Figure 2.—Mass spectrum of 3-deuterioimidazo[1,2-*a*]pyrimidine.

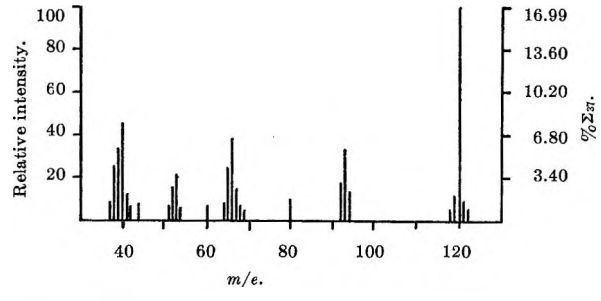


Figure 3.—Mass spectrum of 5-deuterioimidazo[1,2-*a*]pyrimidine.

species **26**. Alternately, the sequence **25** → **23** → **24** is also feasible.

It is of interest to note that the loss of any of the methyl groups in the monomethylpolyazaindenes discussed in this paper is essentially nil. This is in contrast to the relatively facile loss of methyl groups in the various methylpyridines and methylquinolines during electron bombardment, and might be interpreted as being due to the large contribution of resonance structures such as **5**. These contributions would tend to facilitate loss of a hydrogen atom from the methyl group, rather than loss of the methyl group itself.

Experimental Section[7]

The experimental portion of this paper is described in tabular form (Tables II–V) in the following section. Only peaks representing 1% or more of the total ion current are generally listed. The masss pectra of imidazo[1,2-*a*]pyrimidine, 3-deuterioimidazo[1,2-*a*]pyrimidine, and 5-deuterioimidazo[1,2-*a*]pyrimidine are represented in Figures 1, 2, and 3, respectively.

(7) All compounds described in this paper have been prepared by known methods (ref 1 and 2, and papers cited therein). The mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E mass spectrometer. The ionization potential used was 80 eV and the inlet system temperature was set at 180°.

TABLE II

PARENT COMPOUNDS

	Imidazo[1,2-*a*]-pyridine		Imidazo[1,5-*a*]-pyridine		Imidazo[1,2-*a*]-pyrimidine	
m/e	% Σ_{37}	Species[a]	% Σ_{37}	Species[a]	% Σ_{37}	Species[a]
120					2.19	
119	3.05		2.68		28.58	III
118	35.08	I	29.88	II	2.06	
118	1.46		0.81			
93					1.30	
92	2.81		0.85		10.09	**7**
91	8.66	**7**	10.16	**7**	1.18	
90	1.59		1.93			
79	1.10				2.10	**6**
78	11.23	**6**	5.49	**6**		
68					1.26	
66					3.32	
65	1.83		2.44		9.25	**8**
64	5.61	**8**	10.77	**8**	2.52	**27**
63	4.09	**27**	7.12	**27**	0.55	
62	1.46		2.24			
61			1.02			
59.5					1.68	P^{2+}
59	1.59	P^{2+}	1.52	P^{2+}		
53			1.42		2.86	
52	2.81		2.44		2.77	
51	3.66		2.03		1.26	
50	1.46		1.22			
41	2.07		2.13		2.61	
40	1.83		1.22		8.20	
39	3.48		3.86		5.88	
38	3.17		4.27		6.09	
37	1.95		2.03		1.98	

[a] See Schemes I, II, and III.

TABLE III

FIVE-MEMBERED RING METHYL COMPOUNDS

	5-Methylimidazo-[1,2-*a*]pyridine		1-Methylimidazo-[1,5-*a*]pyridine		3-Methylimidazo-[1,5-*a*]pyridine	
m/e	% Σ_3	Species[a]	% Σ_{37}	Species[a]	% Σ_{37}	Species[a]
133	1.64		1.86		1.15	
132	15.36	I	19.59	II	11.99	II
131	19.95	**11, 11′**	12.06	**11, 11′**	7.82	**11, 11′**
106					4.04	**17**
105	1.20	**13**	5.77	**13**	2.82	**13, 18, 18′**
104	1.40	**12**	13.61	**12**	1.69	**12**
92					2.92	**14, 14′**
91					8.92	**7,7′**
79	4.39	**19′**	9.28	**19′**	3.78	**19**
78	6.98	**6**	5.57	**6**	2.22	**6**
77	1.00		2.27		1.82	
76			1.44			
66	2.79	P^{2+}	1.34	P^{2+}	7.25	**15**, P^{2+}
65					5.42	**16**
64	1.40		0.62		4.17	**8**
63	1.60		1.44		4.74	**27**
62					1.88	
52	3.39		4.54		2.48	
51	4.40		5.98		3.34	
50	1.60		3.09		1.88	
41	2.19		0.52		1.56	
40	1.80				3.00	
39	5.00		2.16		6.93	
38	2.59		1.44		3.28	
37	1.40		0.82		1.43	

[a] See Schemes I, II, and III.

TABLE IV
SIX-MEMBERED RING METHYL COMPOUNDS

	5-Methylimidazo-[1,2-a]pyridine[a]		5-Methylimidazo-[1,5-a]pyridine		7-Methylimidazo-[1,2-a]pyrimidine	
m/e	% Σ_{37}	Species[b]	% Σ_{37}	Species[b]	% Σ_{37}	Species[b]
134					2.19	
133	2.68		2.70		25.86	III
132	25.48	I	26.97	II	3.43	**25, 26**
131	14.27	**25, 26**	4.42	**25, 26**		
130	1.02					
118					1.84	
107					1.34	
106	1.02				2.93	**7, 7′**
105	1.53	**7, 7′**	3.76	**7, 7′**	2.39	**23, 24**
104	3.82	**23, 24**	7.63	**23, 24**		
94					1.24	
93					1.69	**6′, 9, 9**
92	1.02	**6′, 9, 9′**	2.87	**6′, 9, 9′**	3.00	*m/e* 93 − H′
91	2.55	*m/e* 92−H	1.66	*m/e* 92−H	0.75	
80					2.19	
79	1.53		2.65		4.97	**8, 20, 21**
78	2.55	**8, 20, 21**	6.32	**8, 20, 21**	1.39	**22**
77	3.06	**22**	4.11	**22**		
76	1.27		1.50			
67					1.79	
66.5					1.24	P^{2+}
66	2.55	P^{2+}	2.21	P^{2+}	2.29	**10**
65	2.21	**10**	2.61	**10**	2.69	
64	1.78		1.90		1.04	
63	2.04		3.45			
62	0.76		1.50			
53	2.04		1.06		3.88	
52	3.31		3.89		5.47	
51	3.57		4.53		3.23	
50	2.04		2.78		1.50	
42	1.27		1.00		1.00	
41	1.27		1.00		1.59	
40	1.78		1.00		3.18	
39	4.33		4.53		4.28	
38	2.04		2.76		1.50	
37	1.27		1.24		0.75	

[a] 6-Methyl, 7-methyl, and 8-methyl are very similar. [b] See Schemes I, II, and III.

Registry No.—I, 274-76-0; I, 3-CH_3, 5857-45-4; I, 5-CH_3, 933-69-7; I, 6-CH_3, 874-38-4; I, 7-CH_3, 874-39-5; I, 8-CH_3, 874-10-2; II, 274-47-5; II, 1-CH_3, 6558-62-9; II, 3-CH_3, 6558-63-0; II, 5-CH_3, 6558-64-1; III, 274-95-3; III, 7-CH_3, 6558-66-3; III, 3-deuterio, 15823-28-6; III, 5-deuterio, 15823-29-7.

TABLE V
METASTABLE IONS

	m* (experimental)	m* (theoretical)	m_1	m_2
Parent Compounds				
Imidazo[1,2-a]pyridine	70.1	70.18	118	91
	51.6	51.56	118	78
	45.0	45.01	91	64
Imidazo[1,5-a]pyridine	70.1	70.18	118	91
	51.6	51.56	118	78
	45.0	45.01	91	64
Imidazo[1,2-a]pyrimidine	71.1	71.12	119	92
	45.9	45.92	92	65
Five-Membered Ring Methyl Compounds				
3-Methylimidazo[1,2-a]pyridine	130.0	130.01	132	131
	103.0	103.01	105	104
	83.5	83.52	132	105
	82.6	82.56	131	104
1-Methylimidazo[1,5-a]pyridine	130.0	130.01	132	131
	103.0	103.01	105	104
	83.6	83.52	132	105
	82.6	82.56	131	104
	59.5	59.44	105	79
	58.5	58.50	104	78
3-Methylimidazo[1,5-a]pyridine	130.0	130.01	132	131
	103.0	103.01	105	104
	82.6	82.56	131	104
Six-Membered Ring Methyl Compounds				
5-Methylimidazo[1,2-a]pyridine	130.0	130.01	132	131
	103.0	103.01	105	104
	82.6	82.56	131	104
6-Methylimidazo[1,2-a]pyridine	130.0	130.01	132	131
	103.0	103.01	105	104
7-Methylimidazo[1,2-a]pyridine	130.0	130.01	132	131
	82.5	82.56	131	104
8-Methylimidazo[1,2-a]pyridine	130.0	130.01	132	131
5-Methylimidazo[1,5-a]pyridine	130.0	130.01	132	131
	103.0	103.01	105	104
	83.5	83.52	132	105
	82.6	82.56	131	104
	58.0	57.94	105	78
	57.0	57.01	104	77
	46.0	45.92	92	65
7-Methylimidazo[1,2-a]pyrimidine	131.0	131.01	133	132
	105.0	104.69	133	118
	84.5	84.48	133	106
	83.5	83.52	132	105
	59.0	58.88	106	79
	47.0	46.84	93	66
	45.9	45.92	92	65

Naphthyridine Chemistry. IX. The Bromination and Amination of the 1,X-Naphthyridines

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The bromination and amination of the 1,X-naphthyridines are reported. The bromination of 1,5-naphthyridine gave the 3-bromo- and the 3,7-dibromo-1,5-naphthyridine. The 3-bromo-, 8-bromo-, and 3,8-dibromo-1,6-naphthyridines were obtained from 1,6-naphthyridine. The 1,7-naphthyridine afforded the 5-bromo and the 3,5-dibromo derivatives. The 3-bromo- and the 3,6-dibromo-1,8-naphthyridines were obtained from 1,8-naphthyridine. The Chichibabin amination of the 1,5-, 1,6-, and 1,8-naphthyridines yielded the 2-amino derivative in each case. The 1,7-naphthyridine gave the 8-amino compound.

The development of facile syntheses[1-3] of 1,5-, 1,6-, 1,7- and of 1,8-naphthyridine has made it possible to study their electrophilic and nucleophilic substitutions in some detail.

We now wish to report the results of bromination and of amination experiments of the 1,X-naphthyridines.

Bromination Studies.—Some time ago, Eisch[4] described a novel method for the introduction of bromine into nitrogen heterocyclic compounds. This method involves the formation of a bromine–heterocyclic compound complex, which, by treatment with pyridine, is "decomposed" to afford a halogenated derivative of the heterocyclic compound. In this fashion, 3-bromoquinoline, 3,8-dibromoquinoline, 3,6-dibromoquinoline, and 3,6,8-tribromoquinoline were obtained, the monobromoquinoline being by far the major product. The bromination of isoquinoline by this procedure afforded the 4-bromoisoquinoline in satisfactory yield.

1,5-Naphthyridine.—The bromination of 1,5-naphthyridine (**1**) by the Eisch procedure afforded a three-component mixture which was separated by column chromatography into unreacted starting material and a monobromo- and a dibromo-1,5-naphthyridine. The pmr spectrum of the monobromo compound (27% yield) showed the presence of an ABX proton system similar to that of the starting material. In addition to this pattern, an AB system (*cf.* Table I) was also present. The size of the coupling constant and the chemical shifts of H_A and of H_B clearly identified the compound as the 3-bromo-1,5-naphthyridine (**5**).

The dibromo compound obtained in 10% yield exhibited a pmr spectrum (*cf.* Table I), which was consistent only with 3,7-dibromo-1,5-naphthyridine (**6**).

Czuba[5] brominated 1,5-naphthyridine in a sealed tube at 135° in H_2SO_4–SO_3, and obtained 7–10% of 3-bromo- and 30–35% of 3,7-dibromo-1,5-naphthyridine. The physical properties of our compounds are identical with those prepared by the Czuba method.

1,6-Naphthyridine.—The bromination of 1,6-naphthyridine (**2**) *via* its bromine complex gave, in addition to unreacted starting material, two monobromo- and one dibromo-1,6-naphthyridine. The pmr spectra were analyzed in a manner similar to that described for the 1,5-naphthyridine products and are recorded in Table I. These data clearly identified the compounds as the 3-bromo- (**7**, 18%), 8-bromo- (**8**, 23% yield), and 3,8-dibromo-1,6-naphthyridine (**9**, 11%).

1,7-Naphthyridine.—The "decomposition" of the bromine complex of 1,7-naphthyridine (**3**) afforded only two bromine-containing products. Elemental analyses identified these compounds as a monobromo and a dibromo derivative of 1,7-naphthyridine. Examination of the pmr spectral data of these two compounds (*cf.* Table I) permitted the identification of the compounds as the 5-bromo-1,7-naphthyridine (**10**) and the 3,5-dibromo-1,7-naphthyridine (**11**), respectively. Whereas the monobromo compound was formed in 25% yield, the dibromo compound was obtained in only 2% yield.

1,8-Naphthyridine.—The bromination of this naphthyridine (**4**) afforded by far the lowest yield of bromo products of any of the 1,X-naphthyridines. Thus, only 5% of the monobromo and 0.5% of the dibromo compound was obtained. The pmr spectra of the substances (*cf.* Table I) identified them as the 3-bromo (**12**) and the 3,6-dibromo compounds (**13**), respectively.

Amination Studies.—The Chichibabin amination of quinoline and of isoquinoline is reported to afford the 2- (and some 4-) amino and the 1-amino compounds, respectively.[6] The application of this amination reaction to the 1,X-naphthyridines became of some special interest for the 1,6- and the 1,7-naphthyridines since these compounds present, *a priori*, two different sites for nucleophilic attack.

1,5-Naphthyridine.—The amination with sodium amide of 1,5-naphthyridine (**1**) has been described by Hart,[7] and the structure of the product, formed in 78% yield, has been shown to be the 2-amino-1,5-naphthyridine (**14**). We were, however, unable to duplicate this amination under the conditions described by Hart. We have now repeated this reaction under conditions which we employed for all of the other 1,X-naphthyridines (potassium amide in liquid ammonia at room temperature) and have obtained the 2-amino-1,5-naphthyridine (**14**) in 33% yield. The pmr spectral data of this compound are reported in Table II and agree with the assigned structure.

1,6-Naphthyridine.—When the reaction conditions used for the amination of 1,5-naphthyridine (**1**) were employed on the 1,6-naphthyridine, there was obtained a monoamino compound whose pmr spectrum is void of the deshielded H_2 proton present in the starting material. The H_5 "singlet" was still present in the amination product. Table II describes the remaining features of the pmr spectrum of this compound which are in agreement with the assigned structure, 2-amino-1,6-naphthyridine (**15**).

(1) W. W. Paudler and T. J. Kress, *J. Org. Chem.*, **32**, 832 (1967).
(2) T. J. Kress and W. W. Paudler, *Chem. Commun.*, **3** (1967).
(3) W. W. Paudler and T. J. Kress, *J. Org. Chem.*, **31**, 3055 (1966).
(4) J. J. Eisch, *ibid.*, **27**, 1318 (1962).
(5) W. Czuba, *Rocz. Chem.*, **37**, 1589 (1963).
(6) F. W. Bergstrom, *J. Org. Chem.*, **3**, 411 (1937).
(7) E. P. Hart, *J. Chem. Soc.*, 1879 (1954).

TABLE I

NMR SPECTRAL DATA OF SOME BROMONAPHTHYRIDINES

Compd[a]	Chemical shifts (τ)							Coupling constants, cps									
	H_2	H_3	H_4	H_5	H_6	H_7	H_8	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,8}$	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
3-Bromo-1,5-naphthyridine (5)	1.04	...	1.44	...	1.04	2.37	1.63	...	2.0	...	0.9	...	...	...	4.3	2.0	8.6
3,7-Dibromo-1,5-naphthyridine (6)	1.03	...	1.45	...	1.03	...	1.45	...	2.0	...	...	...	...	...	...	2.0	...
8-Bromo-1,6-naphthyridine (8)	0.83	2.40	1.70	0.83	...	1.02	...	4.0	1.5	8.3	...	...	...	...	...	...	...
3-Bromo-1,6-naphthyridine (7)	0.97	...	1.70	0.80	...	1.22	2.12	...	1.5	...	0.8	...	...	0.8	...	...	6.0
3,8-Dibromo-1,6-naphthyridine (9)	0.84	...	1.54	0.89	...	1.00	...	...	2.0	...	...	...	...	...	...	...	...
5-Bromo-1,7-naphthyridine (10)	0.95	2.31	1.57	...	1.20	...	0.57	4.0	1.5	8.5	1.0	...	...	...	...	...	...
3,5-Dibromo-1,7-naphthyridine (11)[b]	0.91	...	1.66	...	1.33	...	0.57	...	2.0	...	*b*	...	...	...	...	...	...
3-Bromo-1,8-naphthyridine (12)	0.90	...	1.67	1.89	2.50	0.90	...	...	2.0	...	...	8.0	2.0	...	4.0	...	...
3,6-Dibromo-1,8-naphthyridine (13)	0.91	...	1.73	1.73	...	0.91	...	...	2.0	...	...	...	2.0	...	...	...	...

[a] $CDCl_3$ solutions. [b] This spectrum was obtained with the aid of the C-1024 time averaging computer (Technical Measurements Grp.) and the $J_{2,4}$ coupling constant could only be estimated, while the $J_{4,8}$ coupling constant was only indicated as present by the peak widths.

TABLE II

NMR SPECTRAL DATA OF SOME AMINONAPHTHYRIDINES

Compd[a]	Chemical shifts (τ)							Coupling constants, cps									
	H_2	H_3	H_4	H_5	H_6	H_7	H_8	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,8}$	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
2-Amino-1,5-naphthyridine (14)	...	2.83	1.54	...	1.02	2.04	1.58	...	...	7.0	0.5	...	...	...	4.0	1.5	9.0
2-Amino-1,6-naphthyridine (15)	...	2.40	1.42	0.52	...	1.08	1.74	...	...	9.6	0.5	...	0.8	0.5	...	...	6.9
8-Amino-1,7-naphthyridine (16)	1.02	2.10	1.75	2.82	2.30	...	...	4.0	1.9	8.2	...	7.0	...	...	...	...	...
2-Amino-1,8-naphthyridine (17)	...	2.67	1.70	1.49	2.31	1.17	...	...	...	9.5	...	8.0	1.7	...	5.3	...	...

[a] DTFAA solutions.

TABLE III

TOTAL π-ELECTRON DENSITIES OF THE NAPHTHYRIDINES

Compd	Position							
	1	2	3	4	5	6	7	8
1,5-Naphthyridine (1)	1.42	0.79	0.99	0.89	1.42	0.79	0.99	0.89
1,6-Naphthyridine (2)	1.44	0.77	1.02	0.83	0.77	1.41	0.86	1.04
1,7-Naphthyridine (3)	1.41	0.78	0.98	0.86	0.99	0.89	1.38	0.81
1,8-Naphthyridine (4)	1.45	0.78	1.02	0.85	0.85	1.02	0.78	1.45
2,6-Naphthyridine	0.79	1.38	0.89	0.99	0.79	1.38	0.89	0.99
2,7-Naphthyridine	0.75	1.41	0.86	1.02	1.02	0.86	1.41	0.75

1,7-Naphthyridine.—The sole amination product of 1,7-naphthyridine was a monoamino derivative whose pmr spectrum is void of the H_8 singlet of the starting material. The pmr spectrum (Table II) showed the typical ABX system expected for H_2, H_3, and H_4. In addition to this, an AB system ascribed to H_5 and H_6 was also present. We consequently conclude that this compound is 8-amino-1,7-naphthyridine (**16**). The structure of this compound was also proven by its unequivocal synthesis from 2,3-diaminopyridine *via* the Skraup reaction. This reaction afforded a compound whose physical properties were identical with those of the amination product of 1,7-naphthyridine. This reaction sequence is outlined in Scheme I,[8] p 1386.

1,8-Naphthyridine.—The amination of 1,8-naphthyridine (**4**) again afforded only one monoamino compound. The pmr spectrum (Table II) of this crystalline material was in agreement with that reported by Wibberly and Hawes[9] for the oily product which they obtained from the decarboxylation of 2-amino-1,8-naphthyridine-3-carboxylic acid. The analysis of the pmr spectrum of the amino compound identified it as the 2-amino-1,8-naphthyridine (**17**).

Discussion of the Substitution Reactions.—We have recently described[10] the development of a HMO nitrogen parameter ($\alpha_N = \alpha^\circ_C + 1.1\beta^\circ$) for a series of nitrogen heterocyclic compounds. This parameter was based on the polarographic half-wave reduction potentials of a large number of heterocyclic compounds. The total π electron densities, calculated with the aid of this parameter, for the various naphthyridines are tabulated in Table III.[11]

These ground-state data suggest that electrophilic substitution should occur at position 3 in all of the 1,X-naphthyridines. Since the total π-electron densities at the 8 position in the 1,6- and the 5 position in the 1,7-naphthyridine are slightly higher than the corresponding 3 positions, these positions are also expected to be subject to electrophilic attack.

Except for the lack of detection of any 3-bromo-1,7-naphthyridine all of the expected monobromo(compounds **5**, **7**, **8**, **10**, **12**) and dibromo-1,X-naphthyridines (compounds **6**, **9**, **11**, **13**) were identified.

The total π-electron densities recorded in Table III predict nucleophilic substitution to occur at position 2 of the 1,X-naphthyridines. In addition to this position, the 5 position in the 1,6- and the 8 position in the 1,7-naphthyridine appear to be possible sites for nucleophilic substitution.

With the exception of 1,7-naphthyridine which formed the 8-amino compound exclusively, all of the other 1,X-naphthyridines were aminated at C_2.

The use of total π-electron densities to predict the sites of substitution in aromatic compounds are gen-

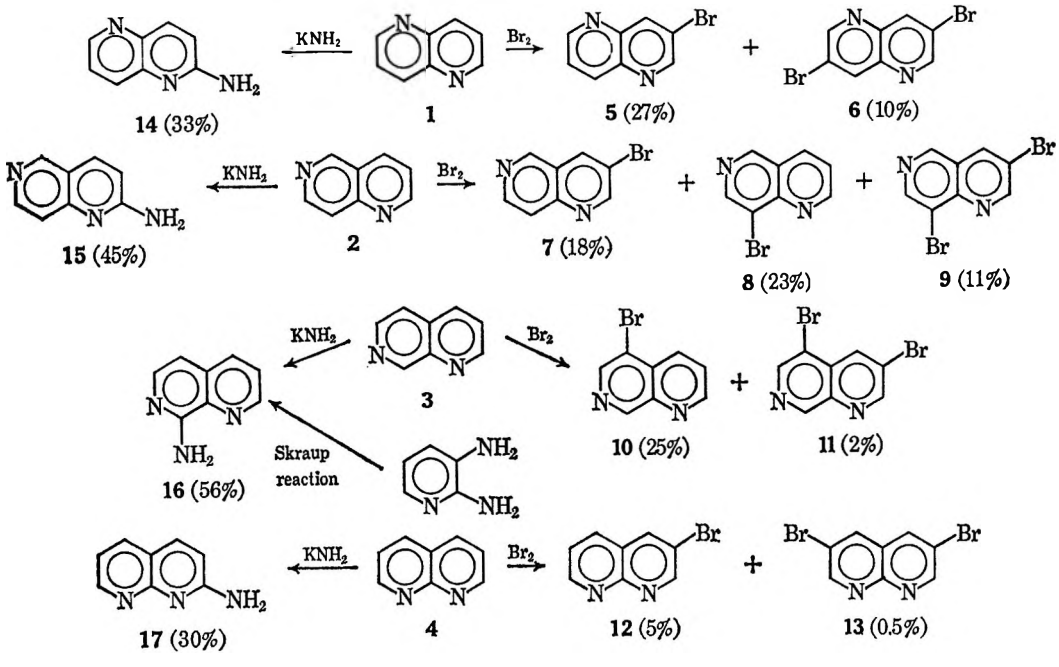
(8) It is of interest to point out that W. Czuba [*Rocz. Chem.*, **41**, 289 (1967)] has shown that one of the products of the Skraup reaction on 3,5-diaminopyridine is the 3-amino-1,5-naphthyridine.

(9) E. M. Hawes and D. G. Wibberly, *J. Chem. Soc., Sect. C*, 1564 (1967).

(10) W. W. Paudler and T. J. Kress, "Some Aspects of the Chemistry of Mono- and Diazanaphthalenes," 1st International Congress of Heterocyclic Chemistry, Albuquerque, N. M., 1967, in press.

(11) See R. G. Shepherd and J. L. Fedrick, *Advan. Heterocycl. Chem.*, **4**, 146 (1965), for an excellent review concerning the reactivity of azines with nucleophiles.

SCHEME I



erally only suitable if there are fairly large numerical differences between the positions under consideration. If the differences are small, these ground-state considerations become less applicable and one must utilize nonground state calculations.

More sophisticated MO calculations might account for the absence of any 3-bromo-1,7-naphthyridine in the electrophilic substitution reactions and the 5-amino-1,6- as well as 2-amino-1,7-naphthyridine in the nucleophilic substitution reactions. The semiempirical rules based on resonance theory described by Shepherd and Fedrick[11] which deal with the Chichibabin amination and related reactions unfortunately do not permit one to account for the facile formation of the 2-amino-1,6-naphthyridine and the lack of formation of any 5-amino derivative other than a possible stability difference between an *ortho,ortho*-quinoidal and a *para,para*-quinoidal transition state. Moreover, the preferred formation of 8-amino-1,7-naphthyridine over the 2-amino-1,7 compound cannot be predicted by these rules.

Experimental Section[12]

General Amination Procedure.—To a dry Carius tube (2 × 60 cm) was added 25 ml of liquid ammonia, followed by a crystal of ferric chloride, and 1.05 g (53 mg-atoms) of freshly cut potassium metal. After the evolution of hydrogen had ceased (about 30 min), 1.09 g (8.45 mmol) of naphthyridine and 1.14 g (11.3 mmol) of potassium nitrate were added simultaneously. The tube was sealed and allowed to stand at room temperature with occasional shaking for 8 days. The cooled tube was opened and a benzene–ethanol (1:1) solution (25 ml) was added in small portions. When the ammonia had evaporated (about 1 hr), water (25 ml) was added, and the organic solvents were removed *in vacuo*. The aminonaphthyridines were then treated as described below.

2-Amino-1,5-naphthyridine (1).—Removal of the organic solvents gave a dark brown gummy solid which was sublimed at 160° (0.1 mm) yielding 365 mg (33%) of white cubes, mp 196–198 (lit.[13] 204–205°).

(12) The nmr spectra were obtained with a Varian A-60 spectrometer The purity of the compounds were ascertained by thin layer chromatography (silica gel G, ether). The mass spectra were determined with a Hitachi Perkin-Elmer RMU-6E mass spectrometer with the liquid sample injection unit at 200° and the ionization voltage at 80 eV. Elemental analyses were performed by Mrs. K. Decker of this department.

2-Amino-1,6-naphthyridine (14).—Removal of the organic solvents gave a brown solid which was filtered, dried, and sublimed at 200° (0.1 mm) affording 402 mg, mp 238–240°, of colorless cubes. One additional sublimation did not alter the melting point.

Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 29.95. Found: C, 66.26; H, 4.81; N, 29.29.

8-Amino-1,7-naphthyridine (16).—Evaporation *in vacuo* of the mixture afforded a brown solid which was collected, dried, and sublimed at 180° (0.1 mm) to give 446 mg (56%) of pale yellow prisms, mp 165–166°.

Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 65.98; H, 4.80; N, 29.05.

2-Amino-1,8-naphthyridine (17).—The organic solvents were removed leaving a brown gum and water. Continuous extraction with chloroform (24 hr) gave, after removal of the organic layer, a yellow oil which could be converted into a semisolid gum after trituration with ether. Heating of the gum at 200° (0.1 mm) gave 350 mg (30%) of pale yellow cubes, mp 141–142°, on the wall of the test tube.

Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86; N, 28.95. Found: C, 66.25; H, 4.92; N, 28.75.

General Bromination Procedure.—To an efficiently stirred solution of 1.30 g (10 mmol) of naphthyridine in 60 ml of carbon tetrachloride was added 2.16 g (12 mmol) of bromine in 6 ml of carbon tetrachloride, and the mixture was refluxed for 1 hr. Pyridine (0.79 g, 10 mmol) in 10 ml of carbon tetrachloride was added over a period of 1 hr to the refluxing solution, and the mixture was heated for an additional 12 hr, cooled, and filtered. The collected solid was digested with 10% sodium hydroxide (100 ml) for 1 hr, and the resulting solution was extracted with chloroform. The chloroform solution and the carbon tetrachloride reaction solution were combined and evaporated *in vacuo*, affording, in each case, a tan solid which was chromatographed on alumina (Brockman grade III) and eluted with 5% ethyl acetate in carbon tetrachloride. The various bromonaphthyridines were then treated in the following manner and are reported in the order in which they were eluted from the chromatography column.

Bromo-1,5-naphthyridines. 3,7-Dibromo-1,5-naphthyridine (6) was obtained as needles (306 mg, 10%) from ethanol, mp 239–240° (lit.[5] 240–241°). **3-Bromo-1,5-naphthyridine (5)**, a white solid (574 mg, 27%), was recrystallized as needles from cyclohexane, mp 106–107° (lit.[5] 107–107.5°). A total of 576 mg (43%) of starting material, **1,5-naphthyridine (1)**, was recovered.

Bromo-1,6-naphthyridines. 3,8-Dibromo-1,6-naphthyridine (9).—The white solid (318 mg, 11%) was recrystallized twice from ethanol affording needles, mp 187–189°.

(13) W. Czuba, *Rec. Trav. Chim. Pays-Bas*, **82**, 988 (1963).

Anal. Calcd for $C_8H_4N_2Br_2$: C, 33.36; H, 1.40; N, 9.73. Found: C, 33.39; H, 1.37; N, 9.63.

3-Bromo-1,6-naphthyridine (7) (372 mg, 18%) was recrystallized twice from cyclohexane giving white crystals, mp 125–126°.

Anal. Calcd for $C_8H_5N_2Br$: C, 45.96; H, 2.41; N, 13.40. Found: C, 45.95; H, 2.45; N, 13.23.

8-Bromo-1,6-naphthyridine (8).—Evaporation of the solvent gave 473 mg (22.6%) of fine cottony needles from cyclohexane, mp 84–86°.

Anal. Calcd for $C_8H_5N_2Br$: C, 45.96; H, 2.41; N, 13.40. Found: C, 45.96; H, 2.51; N, 13.12.

1,6-Naphthyridine (2).—A total of 160 mg (12%) of starting material was recovered.

Bromo-1,7-naphthyridines.—The same conditions were used as in the general procedure but the amounts were as follows: 1,7-naphthyridine (3), 343 mg (2.6 mmol); bromine, 700 mg (3.90 mmol); and pyridine, 240 mg (3.0 mmol).

3,5-Dibromo-1,7-naphthyridine (11).—White crystals [mp 149–151°, mass spectral molecular weight, 288, with the characteristic 1:2:1 ratio (two mass units apart) indicating the presence of two bromine atoms; P, *m/e* 288 (100%)], were obtained in a 27% (16 mg) yield.

Anal. Calcd for $C_8H_4N_2Br_2$: C, 33.36; H, 1.40; N, 9.73. Found: C, 33.06; H, 1.26; N, 9.48.

5-Bromo-1,7-naphthyridine (10).—The white solid was sublimed at 40° (0.1 mm) affording 140 mg (25%) of small fine needles, mp 69–70°.

Anal. Calcd for C_8H_5N Br: C, 45.96; H, 2.41; N, 13.40. Found: C, 45.90; H, 2.57; N, 13.15.

1,7-Naphthyridine (3).—A total of 61 mg (18%) of starting material was recovered.

Bromo-1,8-naphthyridines. 3-Bromo-1,8-naphthyridine (12).—The white solid was sublimed at 100° (0.1 mm) giving 50 mg (4.8%), mp 155–156°, of the monobromo derivative.

Anal. Calcd for $C_8H_5N_2Br$: C, 45.96; H, 2.41; N, 13.40. Found: C, 45.90; H, 2.35; N, 13.30.

3,6-Dibromo-1,8-naphthyridine (13).—The material obtained from the chromatographic column was sublimed at 150° (0.1 mm) affording 6 mg (0.5%) of a white solid, mp 300°.

Anal. Calcd for $C_8H_4N_2Br_2$: C, 33.36; H, 1.40; N, 9.73. Found: C, 33.16; H, 1.30; N, 9.48.

8-Amino-1,7-Naphthyridine (16) **by the Skraup Reaction.**—The previously described procedure[1] for the preparation of 1,8-naphthyridines was employed except that 2,3-diamino- instead of 2-aminopyridine was used. The residue obtained on evaporation of the chloroform extract of the basic reaction mixture, on recrystallization from ethanol, gave 400 mg of a white solid (mp 168–169°). A mixture melting point of this solid with the amination product of 1,7-naphthyridine was not depressed.

Fluorination of Nitroaromatic Amines in Liquid Hydrogen Fluoride and Acetonitrile[1]

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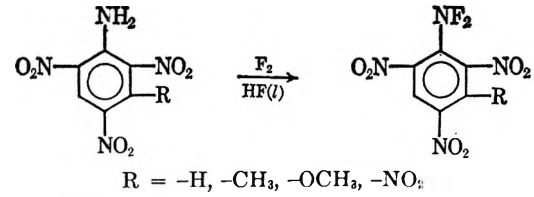
A general synthetic procedure has been found for the preparation of previously unreported nitroaromatic difluoramines. Nitroaromatic monoamines, such as picramide and its analogs, have been converted in high yield into the corresponding difluoramines in liquid hydrogen fluoride and in some cases in organic solvent, such as acetonitrile. Nitroaromatic diamines and triamines undergo similar fluorination reactions. Dinitro-substituted anilines fluorinate in good yield but the amine fluorination is accompanied by ring fluorination *ortho* to the difluoramino group. This reaction and general considerations of aromatic radical stabilization provide evidence for a radical mechanism operating in the fluorination reaction. In addition an unexpected product was obtained in the fluorination of 1,3-dinitro-2,4,6-triaminobenzene, which gave only a small amount of the corresponding trisdifluoramine and a major yield of 1,3-dinitro-2,4,6-tris(difluoramino)-1,2,3,4,5,6-hexafluorocyclohexane. Coupling rather than direct fluorination was obtained with pentafluoroaniline, which yielded bis(pentafluorophenyl)difluorohydrazine by a radical mechanism. The nitroaromatic difluoramino group between adjacent nitro groups was subject to attack by nucleophiles, such as ammonia and water. The synthesis, reaction, and properties of this novel class of compounds are discussed.

There have been relatively few reports of attempts to fluorinate amines by direct elemental fluorination.[2] Among the problems encountered in the direct fluorination of amines are the lack of a suitable solvent medium and decomposition of the reactants owing to the activity of the fluorine. At the least, formation of amine hydrogen fluoride salts can occur as fluorination proceeds, which has on several occasions effectively blocked further reaction. It was felt that, to circumvent these problems, weakly basic amines would be less susceptible to salt formation and, if already substituted with negative groups, they would be less susceptible to oxidation. It also appeared that fluorination in solution would work best, provided reasonable solvation of the starting material and product could be obtained. Since picramide did not form a salt with hydrogen fluoride, it was chosen as an example of a weak base and was fluorinated in liquid hydrogen fluoride, which is an excellent solvent for many nitroaromatic amines. 1-Difluoramino-2,4,6-trinitrobenzene was obtained in good yield, leading us to study the direct fluorination of a variety of nitroaromatic amines to the corresponding nitroaromatic difluoramines, a class of compounds not previously reported. Subsequent research revealed that some organic solvents, particularly acetonitrile, were useful in many cases and provided media for selective fluorinations in solution, a technique not often possible to use.



R = –H, –CH_3, –OCH_3, –NO_2

Results and Discussion

The use of HF as a solvent for direct elemental fluorination of amines is unique and offers several advantages. Anhydrous HF is an excellent solvent for most amines

(1) Presented at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

(2) For reviews on fluorination of organic compounds, see R. Stephens and J. C. Tatlow, *Quart. Rev.* (London), **16**, 57 (1962); J. M. Tedder, *Advan. Fluorine Chem.*, 104 (1960).

and amides. Whereas the amines used in this work are not basic enough to allow salt formation, they are easily solvated. In addition HF allows the use of a much higher concentration of fluorine than that used with organic solvents. The low boiling point of HF (19°) provides for its easy removal during the reaction work-up.

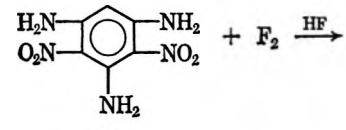
Fluorination of nitroaromatic amines can be carried out in acetonitrile, sulfuric acid, and acetic acid, as well as in HF. Anhydrous HF and acetonitrile are the preferred solvents since they give a cleaner reaction and high yields. Although acetonitrile and fluorine react, the products are volatile and are removed during the reaction work-up. The choice of solvent depends upon the nature of the amine to be fluorinated. Whereas 2,4,6-trinitroaniline and its derivatives can be fluorinated in HF, acetonitrile, or acetic acid without a significant variance in yield, 2,4- and 2,6-dinitroaniline must be fluorinated in acetonitrile, since fluorinations in HF result in complete decomposition. These compounds are basic enough so that partial or complete protonation of the amino group occurs in HF and attack on the aromatic ring occurs. The basic mononitroanilines and aniline cannot be fluorinated in any solvent; in all cases the starting material is destroyed. On the other hand, tetranitro- and pentanitroaniline must be fluorinated in HF; in acetonitrile they are not soluble and no reaction occurs. The solvent properties of HF probably account for its success in these cases. 1,5-Diamino-2,4-dinitrobenzene and 3,5-diamino-2,4,6-trinitrotoluene were consistent with these solvent correlations in that they were more soluble and were best fluorinated in acetonitrile. The only anomaly found was 1,3,5-triamino-2,4-dinitrobenzene, which could be fluorinated in HF but not in acetonitrile. This can be partially explained by the insolubility of the compound in acetonitrile; it is easily soluble in HF. In general, acetonitrile is suitable where solubility of the starting material presents no problem. Anhydrous HF can be used in cases where protonation of the amino group does not occur.

A typical reaction procedure consists of dissolving or suspending the nitroaromatic amine in a suitable solvent and passing a mixture of fluorine in nitrogen through the reaction solution until it becomes lightly colored, after first passing through a dark colored stage. In a few cases the product is insoluble and will precipitate. At this point the solvent is removed, leaving the difluoramino compound in crude state. Finally, purification is by recrystallization or by liquid chromatography using silica gel as the substrate.

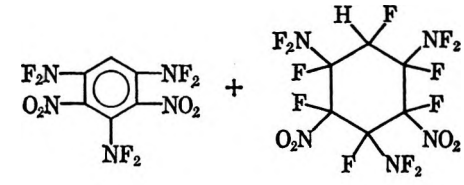
When HF is used as solvent, the fluorinations are carried out in a Kel-F apparatus. When the solvent is acetonitrile, either glass or Kel-F equipment can be used. The conditions for the fluorination of each compound vary, depending upon the solubility, ease of fluorination, etc., of the compound in question. Specific reaction conditions are given in the Experimental Section.

In most instances the desired difluoramino compounds were obtained in good yield. It can be seen from the Experimental Section that nitroaromatic monoamines were easily fluorinated and gave in all but one case stable difluoramino derivatives. Although difluoraminopentanitrobenzene was prepared and isolated in crystalline form, it decomposed in air or under nitrogen within a few minutes. Its structure was confirmed by nmr spectroscopy.

In contrast to nitroaromatic monoamines, the diamines and triamines gave only low yields of difluoramino compounds, along with decomposition products. 2,4-Bis(difluoramino)-1,5-dinitrobenzene could be prepared but had to be separated from its 3-fluoro and 6-fluoro derivatives. When this fluorination was run in acetonitrile both the 3- and 6-fluoro compounds were present; fluorination in HF yielded only the 6-fluoro product as a trace impurity. Fluorination of a compound with completely substituted positions, such as 3,5-diamino-2,4,6-trinitrotoluene, gave a low yield of the bisdifluoramino product. Fluorination of 1,3,5-trinitro-2,4-diaminobenzene and 1,3,5-trinitro-2,4,6-triaminobenzene provided only trace amounts of aromatic difluoramino products; these were detected by ^{19}F nmr spectra of the reaction products, but no compound could be isolated. 1,3,5-Triamino-2,4-dinitrobenzene (I) gave anomalous results not conforming to the patterns established by our other reactions. Fluorination of I was unsuccessful in acetonitrile. However, fluorination in HF gave a small amount of 1,3,5-tris(difluoramino)-2,4-dinitrobenzene (II) and, as the major product, the unexpected compound 1,3,5-tris(difluoramino)-2,4-dinitro-1,2,3,4,5,6-hexafluorocyclohexane (III). Since the more basic character of dinitroanilines was used as the rationale for their inability to be fluorinated in HF, it is surprising that I could be successfully fluorinated. Further, the occurrence of the cyclohexane compound (III) as the major product can only be explained as an addition reaction after initial fluorination. Fluorinated decomposition products often were present in reaction mixtures in this work, but this was the only case in which a stable ring-fluorinated compound was obtained. Although it is known that benzene can react with fluorine in the gaseous state to give perfluorocyclohexene,[3,4] and with COF_3 to give partially fluorinated cyclohexane,[5] the present case appears to be the first instance of ring saturation by fluorine in a liquid medium.



I



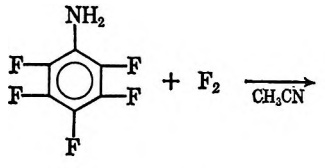
II III

2,2′4,4′,6,6′-Hexanitrodiphenylamine afforded an example of a nonbasic secondary amine. Fluorination in acetonitrile gave the desired 2,2′,4,4′,6,6′-hexanitrodiphenylfluoramine but the fluorination did not proceed in HF. It decomposes within a few days when stored

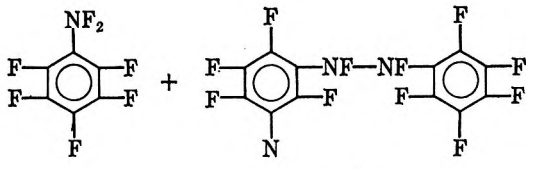
(3) N. Fukahara and L. A. Bigelow, *J. Amer. Chem. Soc.*, **63**, 2792 (1941).
(4) A. R. Gilbett and L. A. Bigelow, *ibid.*, **72**, 2411 (1950).
(5) J. A. Oliver and R. Stevens, *J. Chem. Soc.*, 5491 (1965).

at room temperature but is stable for several months at −18°.

Pentafluoroaniline provided an example of a nonbasic aromatic amine not containing a nitro group. Fluorination of this compound yielded as the major product the coupled compound bis(pentafluorophenyl)difluorohydrazine (VI) and a trace of pentafluorodifluoraminobenzene (V).



IV

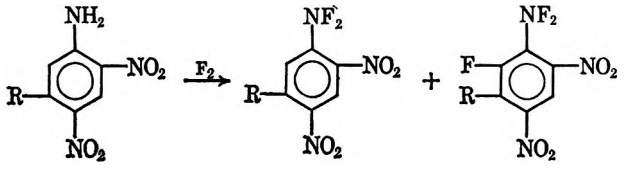


V VI

The fluorination of 2,4,6-trinitroacetanilide was studied briefly to determine whether substituted amines offered any advantage in yield and cleanliness of reaction over free bases. Fluorination in HF afforded 1-difluoramino-2,4,6-trinitrobenzene in 60–75% yield. The reaction proceeded in the same manner as with picramide and no special advantages were noted. However, it is believed that N-acetyl derivatives can be used in place of the parent amine with no loss of efficiency.

The rate and completeness of these fluorinations in solution have not permitted the isolation of intermediates for mechanism studies. Also, whether the fluorination reaction is a radical process or a direct attack of elemental fluorine by an ionic process has not been possible to determine definitely. However, since considerable evidence has been reported substantiating a radical mechanism for other fluorination reactions and satisfactorily answers all questions arising in the present work, we favor it at this time. For example, the fluorination of picramide and of other analogs would take place through abstraction of the amine hydrogen by fluorine radical, followed by fluorination, and a second hydrogen abstraction and fluorination.

Similarly ring fluorination always occurs by a radical reaction when the position *ortho* to the amino group is unsubstituted. Thus, VIIa–c when fluorinated gave the normal difluoramino derivatives, VIIIa–c, plus significant quantities of *o*-fluoro products, IXa–c.

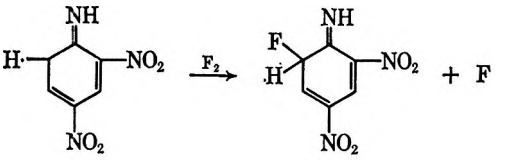


VIIa, R = H; b, R = F; c, R = NH_2

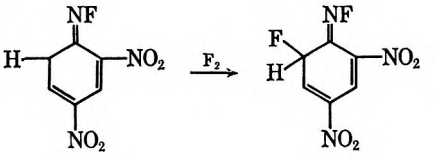
VIIIa, R = H; b, R = F; c, R = NF_2

IXa, R = H; b, R = F; c, R = NF_2

Fluorination of the *ortho* positions can occur through the reaction of intermediate stabilizing radicals such as X or XI shown below with fluorine followed by abstractions of the *ortho* hydrogen and continued fluorination of the amine group. The radical mechanism is further supported by the fact that bis(pentafluorophenyl)difluorohydrazine (VI) is the major product from the fluorination of pentafluoroaniline (IV). This product undoubtedly arises from coupling of two hexafluoroanilyl radicals. Although no coupling products were observed in nitroaromatic amine fluorinations, it seems reasonable that the greater stability of the corresponding radical intermediates, more delocalization of the radical site, and possible steric interferences would not favor the coupling reaction.

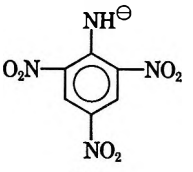


X



XI

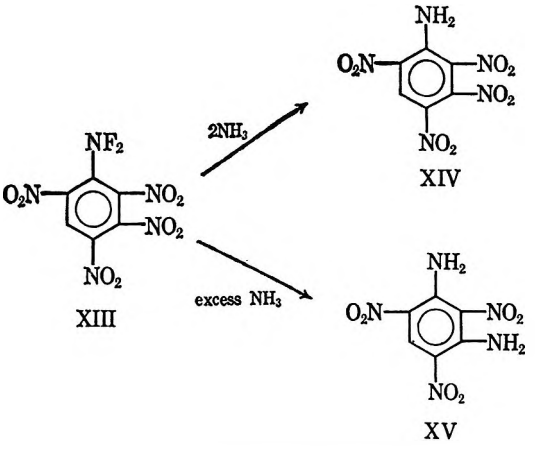
Whereas the radical mechanism is favored, the direct attack of elemental fluorine upon the amines giving rise to stable anions such as XII should not be discounted.



XII

A reaction scheme similar to that for the radical mechanism is quite possible. It is consistent with all questions arising from this work except for the presence of the one coupled product (VI).

A short study of the reactions of nitroaromatic difluoramino compounds was carried out using 1-difluoramino-2,3,4,6-tetranitrobenzene (XIII) as a model compound. When 2 equiv of ammonia were allowed to react, the product was tetranitroaniline (XIV). Addition of an excess of ammonia to XIII gave 1,3-diamino-2,4,6-trinitrobenzene (XV). Thus



XIII XIV XV

the difluoramino group is more easily displaced than nitro by nucleophilic attack. It was also found that the

nitroaromatic difluoramino groups were slowly hydrolyzed by water. When 1-difluoramino-2,4,6-trinitrobenzene was dissolved in 75% aqueous acetonitrile and the increase in picric acid was followed by ultraviolet analysis, it was found that at ambient temperature the difluoramino group was slowly hydrolyzed. Hydrolysis was essentially complete after 12 days.

The nmr spectra of the aromatic difluoramines have very sharp NF_2 peaks occurring in the φ −60 to −68 region. The range of chemical shifts was found to be quite narrow, and substitution influenced the degree of shift only by a small amount. For comparison, the nmr data of the aromatic difluoramines is listed in the experimental section. It can be seen that when an NF_2 group occurs between two nitro groups, the range of chemical shift is φ −61.3 to −63.5, whereas an NF_2 group between a fluoro and a nitro group gives shifts in the φ −62.6 to −63.4 region. When the NF_2 group is flanked by a nitro group and a proton, the range is φ −65.8 to −68.3. This generality, along with splitting patterns, has been found useful for the identification of mixtures of products from fluorination reactions involving nitroaromatic amines. Definite splitting patterns occur between difluoramino groups and *ortho* substituents. The coupling constant for difluoramino groups and fluorine atoms is about 21 cps and for protons about 2 cps. In one case, 1,3-bis(difluoramino)-2,4-dinitrobenzene, coupling occurs between difluoramino fluorines and a proton in the *meta* positions five bonds removed; a value of about 1 cps was determined for this interaction.

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were determined by Stanford University Microanalytical Laboratory. Infrared spectra were run on a Perkin-Elmer Infracord spectrophotometer, and nmr analyses were performed on a Varian HA-100 spectrometer. All τ and φ values for the nmr spectra are reported with respect to tetramethylsilane and fluorotrichloromethane as internal standards. Since many of the compounds prepared in this work are derivatives of trinitrobenzene, they possess the characteristics of high explosives. Although no hazardous incidents have occurred in the present work, we advise that these compounds be handled with caution. The use of plastic in place of metal equipment is recommended.

1-Difluoramino-2,4,6-trinitrobenzene.—A 2.0-g sample of 2,4,6-trinitroaniline was dissolved in 50 ml of anhydrous HF in a Kel-F reactor and fluorinated by bubbling a stream of 60% F_2 in N_2 (62 cc/min) through the solution for 3 hr at −5–0°. As the fluorination proceeded a yellow solid precipitated from the reaction mixture. The solvent was removed by entrainment in N_2, leaving a yellow crystalline solid. This was immediately taken up in CH_2Cl_2 and treated with NaF; the solvent was removed, leaving 2.04 g of crude 1-difluoramino-2,4,6-trinitrobenzene (crude yield, 88%). This was further purified by means of a silica gel column using chloroform as eluent. Elution of the desired compound was detected by spraying a spot of eluate on filter paper with a 0.1% solution of N,N,N′,N′-tetramethyl-*p*-phenylenediamine dihydrochloride (TMPDA reagent) in 50% methylene chloride and ethanol.[6] The spot turned blue immediately and slowly changed to yellow over a 2-min period. Removal of solvent yielded 1.73 g of 1-difluoramino-2,4,6-trinitrobenzene as a light yellow crystalline solid, mp 69°, yield 75%. *Anal.* Calcd for $C_6H_2N_4O_6F_2$: C, 27.27; H, 0.77; N, 21.21. Found: C, 27.22; H, 0.89; N, 20.91.

Picramide can also be fluorinated in acetonitrile and acetic acid in yields of 74 and 64%, respectively.

1-Difluoramino-2,6-dinitrobenzene.—A 0.6-g sample of 2,6-dinitroaniline was dissolved in 15 ml of acetonitrile and was fluorinated at −10 to −5° with a stream of 15% fluorine in nitrogen for 55 min or until the color of the solution changed from orange to yellow. The reaction solution was then poured into 15 ml of diethyl ether and treated with activated charcoal, and the solvent was evaporated, leaving 0.81 g of an orange semisolid. This was taken up in 2 ml of chloroform and passed through a silica gel column using chloroform as solvent. The eluate collected gave a blue to yellow test with the TMPDA reagent.[6] The solvent was then removed *in vacuo*, leaving 0.39 g of a yellow crystalline solid, mp 76–80°. Recrystallization from a 50% chloroform–hexane mixture yielded light yellow needles, mp 91–93°. This compound was identified as 1-difluoramino-2,6-dinitrobenzene by nmr, infrared, and elemental analyses. *Anal.* Calcd for $C_6H_3F_2N_3O_4$: C, 32.86; H, 1.38; N, 19.18. Found: C, 32.61; H, 1.53; N, 19.19.

3-Difluoramino-2,4,6-trinitrotoluene.—A 0.50-g sample of 3-methyl-2,4,6-trinitroaniline dissolved in ~45 ml of anhydrous hydrogen fluoride was fluorinated with a stream of 46% fluorine in nitrogen (56 cc/min) for 30 min at −4 to −6°; a yellow solid precipitated during the fluorination. The solvent was removed, leaving a yellow crystalline solid. This was dissolved in chloroform, filtered to remove a small amount of insoluble material, and treated with sodium fluoride; the solvent was removed *in vacuo*, leaving 0.51 g of a yellow crystalline solid, mp 105–107°. Recrystallization from a chloroform–hexane mixture yielded 0.45 g (78% of theory) of a light yellow crystalline solid, mp 111°, which was identified as 3-difluoramino-2,4,6-trinitrotoluene by elemental analyses and infrared and nmr spectra. *Anal.* Calcd for $C_7H_4F_2N_4O_6$: C, 30.22; H, 1.45; 20.15. Found: C, 30.22; H, 1.35; N, 20.11.

When acetonitrile was used as solvent for this fluorination at −5°, the product was obtained in a 61% yield.

1-Difluoramino-2,4-dinitrobenzene.—Fluorination and isolation procedures were the same as for 1-difluoramino-2,6-dinitrobenzene. The product was a light yellow liquid which contained about 10% 1-difluoramino-6-fluoro-2,4-dinitrobenzene. *Anal.* Calcd for a 9:1 mixture: C, 32.60; H, 1.32; N, 19.02. Found: C, 32.72; H, 1.45; N, 18.90.

1-Difluoramino-5-fluoro-2,4-dinitrobenzene.—Preparative procedure was the same as for 1-difluoramino-2,6-dinitrobenzene. The product was a light yellow crystalline solid, mp 51°. An ^{19}F nmr spectrum showed the presence of a trace amount (<5%) of 1-difluoramino-5,6-difluoro-2,4-dinitrobenzene. *Anal.* Calcd for $C_6H_2F_3N_3O_4$: C, 30.37; H, 0.85; N, 17.73. Found: C, 30.09; H, 0.95; N, 17.80.

3-Difluoramino-2,4,6-trinitroanisole.—Reaction procedure was the same as that for 3-difluoramino-2,4,6-trinitrotoluene. The product was obtained in 77% yield as a yellow liquid. *Anal.* Calcd for $C_7H_4F_2N_4O_7$: C, 28.58; H, 1.36. Found: C, 28.03; H, 1.35.

1-Difluoramino-2,3,4,6-tetranitrobenzene.—Reaction procedure was the same as that for 1-difluoramino-2,4,6-trinitrobenzene except that no external cooling was used (bp HF, +19°). The product was obtained in 75% yield as a yellow crystalline solid, mp 84°. *Anal.* Calcd for $C_6HF_2N_5O_8$: C, 23.32; H, 0.33; N, 22.66. Found: C, 23.45; H, 0.60; N, 22.86.

When the fluorination was run in acetonitrile at 0° a yield of only 30% was obtained.

Difluoraminopentanitrobenzene.—Reaction procedure was the same as that for picramide except that no external cooling was used. The product was stable only in solution and could be detected by its nmr spectrum. When solvent was removed under nitrogen, large orange crystals appeared; however, after a few minutes these became an orange viscous oil.

3,5-Bis(difluoramino)-2,4,6-trinitrotoluene.—Reaction procedure was the same as that used for 1-difluoramino-2,6-dinitrobenzene. The product was obtained in 10% yield as a yellow crystalline solid, mp 143–145°. *Anal.* Calcd for $C_7H_3F_4N_5O_6$: C, 25.56; H, 0.91; N, 21.28. Found: C, 25.39; H, 1.00; N, 21.41.

3-Difluoramino-5-chloro-2,4,6-trinitrotoluene.—Reaction procedure was the same as that used for 1-difluoramino-2,6-dinitrobenzene. The product was obtained in 16% yield as a yellow crystalline solid, mp 149–153°. *Anal.* Calcd for $C_7H_3ClF_2N_4O_6$: C, 26.88; H, 0.97; N, 17.93. Found: C, 27.27; H, 1.19; N, 18.18.

2,2′,4,4′,6,6′-Hexanitrodiphenylfluoramine.—Reaction procedure was the same as that used for 1-difluoramino-2,6-dinitrobenzene. The product was obtained in 54% yield as an orange

(6) A method developed by M. J. Cziesla, Naval Ordnance Station, Indian Head, Md., private communication, Feb 21, 1964.

crystalline solid, mp 102–105° dec. *Anal.* Calcd for $C_{12}H_4FN_7O_{12}$: C, 30.26; H, 0.85. Found: C, 30.69; H, 0.98.

Fluorination of 1,5-Diamino-2,4-dinitrobenzene.—A 1.50-g sample of 1,5-diamino-2,4-dinitrobenzene was suspended in a 50 ml of acetonitrile and fluorinated at 0° with a stream of 20% fluorine in nitrogen (58 cc/min) for 105 min or until all of the solid starting material had dissolved and the solution turned light yellow. The reaction mixture was then poured into 100 ml of diethyl ether and treated with sodium fluoride, and the solvent was removed *in vacuo*, leaving 2.70 g of an orange liquid. This was dissolved in 1 ml of benzene and passed through a silica gel column using benzene as solvent. The eluate which was collected gave a positive difluoramino test with the TMPDA reagent. The solvent was removed, leaving 0.53 g of a light yellow semisolid. Recrystallization from a solution of 40% ether in hexane yielded 0.42 g of a yellow crystalline solid, mp 85° to 93°. An nmr spectrum of the solid showed that it consists of approximately 60% 1,5-bis(difluoramino)-2,4-dinitrobenzene, A, and 40% 1,5-bis(difluoramino)-2,4-dinitro-6-fluorobenzene, B. A trace of 1,5-bis(difluoramino)-2,4-dinitro-3-fluorobenzene was also present.

The two major components were separated and purified by passing the mixture through a silica gel column using a solution of 40% benzene in hexane as eluent. Product B eluted first, closely followed by A. However, they could be differentiated by using the TMPDA reagent, since product A gave a darker yellow spot than product B. Removal of solvent left pure samples of 0.24 g of A, mp 112°, and 0.16 g of B, mp 122°. Both products could be recrystallized from a 50% mixture of chloroform in hexane. *Anal.* Calcd for $C_6H_2F_4N_4O_4$ (A): C, 26.67; H, 0.75; N, 20.76. Found: C, 26.42; H, 0.75; N, 21.17. *Anal.* Calcd for $C_6HF_5N_4O_4$ (B): C, 25.02; H, 0.35; N, 19.45. Found: C, 25.01; H, 0.44; N, 19.59.

Fluorination of 1,3,5-Triamino-2,4-dinitrobenzene.—A 0.8 g sample of 1,3,5-triamino-2,4-dinitrobenzene was dissolved in 40 ml of anhydrous HF and fluorinated at −38° with a stream of 70% fluorine in nitrogen for 115 min or until the color of the reaction solution changed from orange to light yellow. The solvent was removed by entrainment in nitrogen, and the resulting green liquid was taken up in methylene chloride; this was treated with activated charcoal and the solvent was removed *in vacuo*, leaving 1.12 g of a light green liquid. This liquid was dissolved in chloroform and passed through a silica gel column using chloroform as solvent. The eluate was collected in two portions; one (A) gave a blue to yellow test with the TMPDA reagent, and the second portion (B) gave a spot which remained blue. Removal of solvent from A left 0.09 g of a light yellow solid, mp 46–53°. Recrystallization from a chloroform–hexane mixture gave a light yellow crystalline compound melting at 54–56°; this was 1,3,5-tris(difluoramino)-2,4-dinitrobenzene. *Anal.* Calcd for $C_6HF_6N_5O_4$: C, 22.44; H, 0.31; N, 21.82. Found: C, 22.18; H, 0.39; N, 22.20.

Evaporation of the solvent from fraction B left 1.02 g of a pale blue liquid which was tentatively identified as 1,3,5-tris(difluoramino)-2,4-dinitro-1,2,3,4,5,6-hexafluorocyclohexane arising from the saturation of the benzene ring of product A by fluorine. Elemental analysis and infrared and nmr spectra support this conclusion. *Anal.* Calcd for $C_6HF_{12}N_5O_4$: C, 16.56; H, 0.23; N, 16.10. Found: C, 16.91; H, 0.2; N, 15.57.

An ^{19}F spectrum of this product in $CDCl_3$ showed the data listed in Table I.

Nmr Data for Aromatic Difluoramino Compounds.—Listed below are the nmr data for the difluoramino nitroaromatic compounds synthesized in this work. The spectra were run on a Varian HA-100 spectrometer and all φ and τ values are reported with respect to $CFCl_3$ and TMS, respectively. Where no designation of splitting pattern is mentioned, the signal is a singlet.

1-Difluoramino-2,4-dinitrobenzene showed an absorption at φ −66.9 (−NF_2). 1-Difluoramino-2,4-dinitro-6-fluorobenzene had signals at φ −62.6 (−NF_2), doublet, $J_{NF,F}$ = 22 cps; +102.3 (−F), triplet of doublets, $J_{F,NF}$ = 21 cps, $J_{F,H}$ = 10 cps. 1-Difluoramino-2,4-dinitro-5-fluorobenzene had signals at φ −65.8 (−NF_2); +103.2 (−F), multiplet; τ 1.21 (−H, 3), doublet, 7 cps; 2.04 (−H, 6), doublet to triplets, $J_{H,F}$ = 10 cps, $J_{H,NF}$ = ~1.5 cps. 1-Difluoramino-2,4-dinitro-5,6-difluorobenzene had signals at φ −62.7 (−NF_2), doublet, $J_{NF,F}$ = 21 cps; +126.5 (−F, 5), doublet, $J_{F,F}$ = 21 cps; +123.9 (F, 6), quartet, J = 21 cps. 1-Difluoramino-2,6-dinitrobenzene showed absorptions at φ −63.5 (−NF_2); τ 2.02 (H, ring). 1-Difluoramino-2,4,6-trinitrobenzene had signals at φ −62.1 (−NF_2); τ 1.08 (H, ring). 1,5-Bis(difluoramino)-2,4-dinitrobenzene showed absorptions at φ −68.3 (−NF_2); τ 1.51 (H, 3), quintet, $J_{H,NF}$ = ~1 cps; 1.35 (H, 6), quintet, $J_{H,NF}$ = ~2 cps. 1,5-Bis(difluoramino)-2,4-dinitro-6-fluorobenzene had signals at φ −63.4 (−NF_2), doublet, $J_{NF,F}$ = 21.5 cps; +104.2 (−F), quintet, $J_{F,NF}$ = 21.5 cps; τ 2.72 (−H), singlet. 1,5-Bis(difluoramino)-2,4-dinitro-3-fluorobenzene had signals at φ −67.4 (−NF_2), singlet; 102.6 (−F), singlet. 3-Difluoramino-2,4,6-trinitrotoluene had signals at φ −62.8 (−NF_2); τ 7.42 (−CH_3); 1.48 (−H, ring). 3-Difluoramino-2,4,6-trinitroanisole showed absorptions at φ −61.8 (−NF_2); τ 5.96 (−CH_3); 1.50 (−H, ring). 1-Difluoramino-2,3,4,6-tetranitrobenzene had signals at φ −61.3 (−NF_2); τ 1.22 (−H, ring). 1-Difluoramino-2,3,4,5,6-pentanitrobenzene, 3-difluoramino-5-chloro-2,4,6-trinitrotoluene, and 3,5-bis(difluoramino)-2,4,6-trinitrotoluene had signals at φ −62.0 (−NF_2), −62.5 (−NF_2), and −62.5 (−NF_2), respectively. 1,3,5-Tris(difluoramino)-2,4-dinitrobenzene showed absorptions at φ −63.5 (−NF_2, 1); −68.2 (−NF_2, 3, 5). N-fluoro-1,1′,2,2′,3,3′-hexanitrodiphenylamine had a signal at φ −15.4 (−NF).

TABLE I

Peak, φ	Assignment	Relative size
−23.9, multiplet	1,3,5-NF_2	6
111.5, doublet of multiplets	6-CF	1
128.1, broad singlet	1,5-CF	2
151.0, triplet	3-CF	1
157.9, broad singlet	2,4-CF	2

Registry No.—Hydrogen fluoride, 7664-39-3; acetonitrile, 75-05-9; II, 15892-90-7; III, 15815-99-3; XIII, 15733-90-1; 1-difluoramino-2,4-dinitrobenzene, 15733-91-2; 1-difluoramino-2,4-dinitro-6-fluorobenzene, 15733-92-3; 1-difluoramino-2,4-dinitro-5-fluorobenzene, 15733-93-4; 1-difluoramino-2,4-dinitro-5,6-difluorobenzene, 15734-01-7; 1-difluoramino-2,6-nitrobenzene, 15733-94-5; 1-difluoramino-2,4,6-trinitrobenzene, 15733-96-7; 1,5-bis(difluoramino)-2,4-dinitrobenzene, 15733-95-6; 1,5-bis(difluoramino)-2,4-dinitro-6-fluorobenzene, 15733-97-8; 1,5-bis(difluoramino)-2,4-dinitro-3-fluorobenzene, 15733-98-9; 3-difluoramino-2,4,6-trinitrotoluene, 15734-02-8; 3-difluoramino-2,4,6-trinitroanisole, 15733-99-0; 1-difluoramino-2,3,4,5,6-pentanitrobenzene, 15734-00-6; 3-difluoramino-5-chloro-2,4,6-trinitrotoluene, 15735-52-1; 3,5-bis(difluoramino)-2,4,6-trinitrotoluene, 15816-00-9; 2,2′,4,4′,6,6′-hexanitrophenylfluoramine, 15816-01-0.

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Dehydrofluorination of Amine Metalloid Fluorides. II.[1a] The Reaction of Phosphorus Pentafluoride with Primary Amines[1b]

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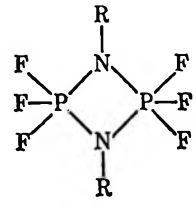
Phosphorus pentafluoride is shown to react with primary amines to give a variety of products depending upon the amine, solvent, and reaction conditions. An adduct was isolated from aniline, 2,6-dimethylaniline, and *n*-propylamine but could not be isolated from 2,6-diethylaniline or isopropylamine under the mildest conditions employed (0–10°) in heptane or benzene. Disproportionation of the adduct from aniline and *n*-propylamine in the presence of phosphorus pentafluoride gave the corresponding amine hexafluorophosphate salt and diazadiphosphetidine. Disproportionation of the adduct from more hindered amines such as 2,4-dimethylaniline, 2,6-dimethylaniline, and 2,6-diethylaniline gave the corresponding amine hexafluorophosphate salt and aminophosphorus tetrafluoride. Addition of triethylamine (or other tertiary amine) to the reaction of primary amines with phosphorus pentafluoride causes formation of diazadiphosphetidines from hindered as well as unhindered amines, with formation of the tertiary amine hexafluorophosphate salt. The infrared and ^{19}F nmr spectra are discussed for certain of the products. Dehydrofluorination of ammonia–phosphorus pentafluoride with triethylamine or diisopropylethylamine–phosphorus pentafluoride gives small yields of phosphonitrilic fluorides but the major product is an incompletely dehydrofluorinated oil.

This paper reports that portion of a general study of the dehydrofluorination of metalloid fluoride–amine systems involving the reactions of phosphorus pentafluoride with primary amines. Phosphorus pentafluoride is known to be a strong Lewis acid and thus to form adducts with Lewis bases.[2] These adducts are generally less stable than the corresponding boron trifluoride adducts possibly because of crowding around the phosphorus atom in the hexacoordinated state. The literature on phosphorus pentafluoride, as thoroughly reviewed by Schmutzler,[3,4] contains very little on the reaction of phosphorus pentafluoride and primary amines in marked contrast to the well-studied reactions of primary amines with phosphorus pentachloride.[5] Several primary amine adducts of phosphorus pentafluoride were reported[6] as curing agents for epoxy resins but synthetic and structural details are lacking. Phosphorus pentafluoride has been reported recently[7] to react with secondary amines according to eq 1. Tertiary amines form adducts with

$$R_2NH + PF_5 \longrightarrow R_2NPF_4 \text{ or } (R_2N)_2PF_3 + R_2NH_2{}^+PF_6{}^- \quad (1)$$

phosphorus pentafluoride but these are often highly dissociated.[2]

Our research shows that phosphorus pentafluoride reacts with primary amines (at times in the presence of a tertiary amine) to give 2,2,2,4,4,4-hexafluoro-2,2,4,4-tetrahydro-1,3-diorgano-1,3,2,4-diazadiphosphetidines (I), hereafter termed the cyclic dimer for simplicity, aminophosphorus tetrafluorides (II), and amine hexafluorophosphate salts (III), depending upon reaction conditions described later. There were indications that products such as $(RNH)_nPF_{5-n}$ and $RNH_3{}^+PF_5NHR^-$ may be formed but these were not



I

$RNHPF_4$ II

$RNH_3{}^+PF_6{}^-$ III

characterized. The cyclic dimer (R = Ph) was also formed by dehydrofluorination of aniline–phosphorus pentafluoride with the adduct of boron trifluoride and diisopropylethylamine.

Amine hexafluorophosphate salts are well known, although there are surprisingly few reports of such salts of primary amines. There are no reports of primary aminophosphorus tetrafluorides in the literature. The cyclic dimer is well known for the corresponding phosphorus chlorine compounds[5] and there have been scattered reports of the fluorinated cyclic dimer. The fluorinated cyclic dimer has been prepared previously by (1) the reaction of phosphorus pentafluoride with heptamethyldisilazane,[8] (2) the fluorination of the chlorinated dimer,[9] or (3) the reaction of trimethylamine, methylamine, and phosphorus pentafluoride.[9] Procedure 3, which is analogous to our reactions using triethylamine, has not appeared in the published literature and became known to us after our research was completed.[4]

Results

A.—The reaction of phosphorus pentafluoride with primary amines is not so straightforward as the reaction of boron trifluoride with primary amines. Whereas boron trifluoride and amines almost invariably give the simple adduct,[10] the product isolated from the reaction of phosphorus pentafluoride and primary amines depends upon the amine and reaction conditions employed.

Isolation of the adduct required the proper combination of reaction time, temperature, and poor solvent for

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the adduct, rapid addition of phosphorus pentafluoride, and/or less than stoichiometric quantities of phosphorus pentafluoride. The reaction with aniline was studied in some detail. At 6° the adduct was formed with very little side reaction upon either slow or rapid addition of phosphorus pentafluoride to the reaction mixture. However, at 25° rapid addition of phosphorus pentafluoride was necessary to minimize reaction of the adduct with excess aniline. Reaction of the adduct with aniline is postulated to occur according to eq 2 and 3.

$$RNH_2 \cdot PF_5 + RNH_2 \longrightarrow RNH_3{}^+RNHPF_5{}^- \quad (2)$$

$$3RNH_2 \cdot PF_5 + RNH_2 \longrightarrow 2RNH_3{}^+PF_6{}^- + (RNH)_2PF_3 \quad (3)$$

The aniline adduct could not be isolated when a marked deficiency of phosphorus pentafluoride was added and if the mixture was stirred several hours before work-up. Similarly the isolated aniline adduct was shown to react at 25° with excess aniline. The aniline adduct was similarly reactive when stirred at 25° in phosphorus pentafluoride which appeared to catalyze its disproportionation according to eq 4.

$$6RNH_2 \cdot PF_5 \xrightarrow{PF_5} (RNPF_3)_2 + 4RNH_3{}^+PF_6{}^- \quad (4)$$

n-Propylamine also reacted according to eq 4 in excess phosphorus pentafluoride. The impure adduct was isolated when a stoichiometric quantity of phosphorus pentafluoride was used. Side reactions according to eq 2 and 3 were indicated. No adduct was isolated from the isopropylamine; reactivity according to eq 2 or 3 was indicated.

The hindered amines 2,6-diethyl- or 2,6-dimethylaniline reacted in a more straightforward manner. Although no adduct could be isolated from 2,6-diethylaniline, a product postulated to be the adduct was formed from 2,6-dimethylaniline by using a deficiency of phosphorus pentafluoride, a poor solvent for the adduct (heptane), and a short reaction time, and immediate separation of the adduct. Both amines reacted with either an excess or a deficiency of phosphorus pentafluoride according to eq 5. The adduct from these highly

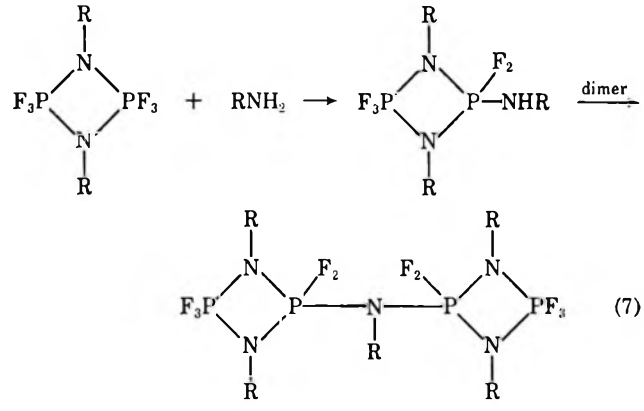
$$2RNH_2 + 2PF_5 \longrightarrow RNH_3{}^+PF_6{}^- + RNHPF_4 \quad (5)$$

hindered amines then is not reactive toward excess amine, probably because of steric effects. Cyclic dimer is not formed even when the reaction mixture is refluxed for several hours. Failure to isolate the cyclic dimer does not arise from steric instability of the cyclic dimer since the cyclic dimers are formed in high yield in presence of tertiary amines as described later. Consequently, the lack of cyclic dimer formation must indicate an inability of the intermediate anilinophosphorus pentafluoride to react with itself or with adduct to form cyclic dimer.

B.—Mixtures of primary amines and tertiary amines (usually triethylamine) in benzene react with phosphorus pentafluoride according to eq 6. The reaction, as indicated by isolation of triethylammonium hexafluorophosphate and soluble dehydrofluorination product, is almost quantitative. Small quantities of

$$2RNH_2 + 4Et_3N + 6PF_5 \longrightarrow (RNPF_3)_2 + 4Et_3NH^+PF_6{}^- \quad (6)$$

partially dehydrofluorinated product $RNHPF_4$ were found at times. The cyclic dimer is formed from all primary amines investigated even those with high steric requirements. Unhindered primary amine phosphorus pentafluoride adducts give, in nearly quantitative conversion, approximately equal quantities of cyclic dimer and higher condensation products. By contrast, the hindered 2,6-diethylaniline gives nearly quantitative yield of cyclic dimer. The greater yield of cyclic dimer from the sterically hindered amines reflects either the greater steric resistance to the formation of larger rings or linear chains or steric resistance to the condensation of the cyclic dimer with excess amine according to eq 7. Thus cyclic dimer

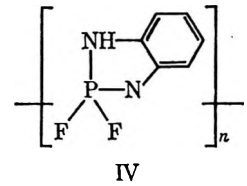


(R = Ph) was shown to react with aniline to give higher condensation products. By contrast the cyclic dimer from 2,6-diethylaniline was recovered unchanged after being refluxed in benzene with excess 2,6-diethylaniline.

A detailed study of the efficiency of different tertiary amines was not made. Triethylamine was used in most instances. The relatively low melting point of the by-product triethylammonium hexafluorophosphate was a disadvantage in some instances since the salt served as a solvent for the dehyrofluorination product. In this respect diisopropylethylamine, which forms a much higher melting salt, gave much less trouble. Presumably other tertiary or secondary amines would function as the dehydrofluorinating agent.

C.—Dehydrofluorination was caused by amine complexes of other metalloid fluorides. Thus aniline phosphorus pentafluoride is dehydrofluorinated by the adduct of diisopropylethylamine boron trifluoride to give the cyclic dimer and other dehydrofluorination products.

D.—An attempt to dehydrofluorinate the *o*-phenylenediamine phosphorus pentafluoride adduct with triethylamine phosphorus pentafluoride, to give phosphobenzimidazole derivatives of type IV analogous to borabenzimidazole derivatives, was not successful. Although dehydrofluorination occurred, no well-defined aromatic products could be isolated.



IV

E.—Dehydrofluorination of ammonia–phosphorus pentafluoride with either the triethylamine or diisopropylethylamine adducts of phosphorus pentafluoride

gives somewhat variable results. At times small yields of phosphonitrilic fluorides $(NPF_2)_n$ are obtained. However, the main product is an oil not readily separated from the by-product $Et_3NH^+PF_6$ salt. This oil had strong absorption at 1280–1250 and at 910–930 cm^{-1}. The oil likely contained incompletely dehydrofluorinated NH_3–PF_5 products, perhaps of the type $+NHPF_3+$. Since intermediate products of the type NH_2PF_4 may be volatile, more vigorous reactions in sealed systems is indicated.

Discussion

In summary the reaction of phosphorus pentafluoride with primary amines is relatively complex, particularly for nonhindered amines. The complexity of the reactions as described is probably due at least in part to the manner in which the reactions were run since the phosphorus pentafluoride was added to the amine, meaning that excess amine was present during most of the reaction. The reaction products from aniline, *e.g.*, adduct or cyclic dimer, were shown to be reactive to excess aniline. Similar reactivity of other primary amines such as *n*-propylamine was indicated. Thus revising the experimental setup so that primary amine is not present with the reaction products should give more straightforward results. Thus amine might be added slowly to a solution of the phosphorus pentafluoride–tetrahydrofuran adduct (or other suitable source of phosphorus pentafluoride).

No attempt was made to prepare and identify products of the type $(RNH)_nPF_{5-n}$. However products of this type were indicated to be present in reactions involving nonhindered amines such as aniline. Previous research[7] with secondary amines had indicated substitutions on the phosphorus of only one and two amino groups. The less hindered primary amines may give higher substitution and should be a fruitful area for further study.

Properties

A. 2,2,2,4,4,4-Hexafluoro-2,2,4,4-tetrahydro-1,3-organo-1,3,2,4-diazadiphosphetidine (Cyclic Dimer).—The cyclic dimers $(RNPF_3)_2$ were solids (except where R = *n*-propyl) sufficiently volatile to be purified by sublimation at reduced pressure. Sublimation of 2,6-disubstituted phenyl derivatives left negligible residue, but less hindered phenyl derivatives left resinous materials of higher molecular weight. The more hindered derivatives were thus more resistant to rearrangement to higher molecular weight products. This is consistent with the greater yields of cyclic dimer, compared with higher molecular weight resinous products, isolated from the preparations from 2,6-disubstituted anilines. The cyclic dimers in which R is aromatic could also be purified readily by recrystallization from dried aromatic solvents, such as benzene, in which they were only sparingly soluble at room temperature. The solubility of the products in polar solvents such as tetrahydrofuran was greater, but these were not used for crystallization because of their tendency to pick up moisture which reacts with the cyclic dimer. The compounds reported, except for the more volatile R = *n*-propyl one, did not fume and could be handled in air. However, exposure to air had to be brief since the products were attacked by atmospheric moisture. Analytical samples were handled under nitrogen. The melting points and volatilities are indicated in Table I.

TABLE I
MELTING POINT AND VOLATILITY OF CYCLIC DIMERS $(RNPF_3)_2$

No.	R	Mp, °C	Sublimation temperature[a] or bp, °C (mm)
1	C_6H_5	198–205	Sublimes at 110–130 (0.4)
2	2,4-$Me_2C_6H_3$	164–168	Sublimes at 140–150 (0.4)
3	2,6-$Me_2C_6H_3$	255–257	Sublimes at 130 (0.05)
4	2,6-$Et_2C_6H_3$	151–152	Sublimes at 125 (0.025)
5	*n*-C_3H_7	4–7	Boils at 41 (4)
			Boils at 70–72 (21)
6	*t*-C_4H_9	70–72	Sublimes at 70 (4)

[a] The sublimation temperature refers to the bath temperature.

The chemical reactivity of the cyclic dimers was not studied in detail. However, the steric requirements of the organic group affected their stability. Thus cyclic dimer (R = Ph) reacted with aniline to form higher condensation products while cyclic dimer (R = 2,6-$Et_2C_6H_3$) did not react with excess 2,6-diethylaniline.

B. Aminophosphorus Tetrafluorides.—The aminophosphorus tetrafluorides $(RNHPF_4)$ had about the same volatility as the parent amine. Except where R is 2,6-diethylphenyl or 2,6-dimethylphenyl they decomposed to cyclic dimer (and other products) and amine hexafluorophosphate too rapidly for satisfactory analysis to be obtained. Small amounts of a product believed to be anilinophosphorus tetrafluoride were formed in the reaction with aniline, but this product was not characterized except by its infrared spectrum and is not included in Table II. The aminophosphorus tetrafluorides were readily soluble in aromatic or aliphatic hydrocarbon solvents and did not fume in air, except where R = *i*-C_3H_7. However, they were hydrolyzed slowly and exposure to atmospheric moisture was minimized. Properties are listed in Table II.

TABLE II
MELTING POINT AND VOLATILITY OF AMINOPHOSPHORUS TETRAFLUORIDES $(RNHPF_4)$

No.	R	Mp, °C	Sublimation temperature[a] or bp, °C (mm)
1	2,4-$Me_2C_6H_3$	32–34	Boils at 42–44 (0.5)
2	2,6-$Me_2C_6H_3$	60–62	Sublimes at 60 (0.5)
3	2,6-$Et_2C_6H_3$	15–17	Boils at 63 (0.5)
4	*i*-C_3H_7		Boils at 37 (750)

[a] Sublimation temperature refers to bath temperature.

C. Adducts and Salts.—Several amine–phosphorus pentafluoride adducts were prepared as intermediates during the course of the investigation. The amine–phosphorus pentafluoride adducts were of somewhat limited stability and their isolation where bulky amines were used was not possible. Although the adducts were not well characterized and analyses were obtained in only a few instances, their identification as adducts is believed to be adequate, based on (1) the infrared spectra of the products as discussed in that section and (2) the stoichiometry of the reaction system. The adduct was considered to be formed only if no other products were present except unreacted amine and both amine and adduct were present in the correct

weight ratio. Disproportionation of the adduct yields salt and dehydrofluorination products; hence the absence of these indicates the adduct formed has not reacted further. The primary amine adducts were slightly soluble to somewhat soluble in aromatic solvents. They did not fume in the atmosphere but did decompose; thus they could not be stored in glass because of severe etching.

The stability of the adducts which could be isolated was dependent upon the method of preparation and purity. A well-washed adduct of aniline (a) could be partially recovered after 6 hr of reflux in benzene and was only slightly decomposed on several days' storage while a sample (b) prepared in excess phosphorus pentafluoride decomposed in 2 days to salt and cyclic dimer. The adducts rearranged upon heating. The aniline adduct (b), for example, gave salt and cyclic dimer, when heated to 120° at reduced pressure. However, another sample of the aniline adduct (a) gave salt and a product postulated to be $PhNHPF_4$ when heated. Similarly the adduct from *n*-propylamine formed salt and dehydrofluorination products when heated.

A number of amine hexafluorophosphates were isolated as by-products during these reactions. These salts were not completely characterized by analysis although they were analyzed for the PF_6^- group by the Nitron reagent. The characterization as salts is warranted by these analyses and the following points: (1) infrared analysis as described in a following section, (2) solubility in water and insolubility in hydrocarbon, and (3) stoichiometry of the reaction. The salt was considered to be formed only if a corresponding quantity of characterized dehydrofluorination products was isolated. Their physical properties are given in Table III.

TABLE III

PROPERTIES OF AMINE–PHOSPHORUS PENTAFLUORIDE ADDUCTS AND AMINE HEXAFLUOROPHOSPHATE SALTS

No.	Amine	Adduct	Salt
1	$C_6H_5NH_2$	Mp 175–210° dec	Mp 250°, sublimes at 220° (1 atm); 140–160°(0.5 mm)
2	$2,4\text{-}Me_2C_6H_3NH_2$	Not isolated	Mp 194–198°
3	$2,6\text{-}Me_2C_6H_3NH_2$	Discolors at 200°, mp 235–240° dec	Mp 207°, sublimes at 160–180 (0.5 mm)
4	$2,6\text{-}Et_2C_6H_3NH_2$	Unstable	Mp 152–172°
5	$o\text{-}C_6H_4(NH_2)_2$	Mp 126–140°	
6	$n\text{-}C_3H_7NH_2$	Mp 110–120°, very hygroscopic	Mp 187–183°
7	Et_3N	Unstable	Mp 85–88°
8	$i\text{-}Pr_2EtN$	Unstable	Mp 195–204°
9	$i\text{-}PrNH_2$	Unstable	Mp 165–172°

^{19}F Nmr spectra.—The preference of compounds of the type $(RNPX_3)_n$ to exist as dimers rather than as trimers or tetramers as found, for example, for the phosphonitrilic compounds, raises interesting questions about the cyclic bonding orbitals used by the phosphorus atom. Formation of the cyclic phosphorus–nitrogen bonds from one axial and one equatorial bond from the ordinary pentacovalent phosphorus trigonal bipyramid would give a strain-free N–P–N bond angle of 90°. The three fluorine atoms should be at two equatorial and one axial positions and be readily distinguished by ^{19}F nmr analysis. Similarly, formation of the cyclic bonds from two equatorial phosphorus orbitals (which would introduce considerable strain) would leave one equatorially and two axially substituted fluorines, again distinguished by ^{19}F nmr spectroscopy. The analogous dimer $(MeNPCl_3)_2$ has the former configuration.[11] However, the cyclic dimers examined had only a single ^{19}F band indicating that the phosphorus fluorine bonding orbitals are being rapidly equilibrated. The phosphorus fluorine coupling constants for the cyclic dimers are shown in Table IV.

TABLE IV

P–F COUPLING CONSTANTS FOR DIMERS $(RNPF_3)_2$

R	P–F, cps
$n\text{-}C_3H_7$	897.2
C_6H_5	918.2
$2,4\text{-}Me_2C_6H_3$	914.0
$2,6\text{-}Me_2C_6H_3$	900

The coupling constants are intermediate between the normal equatorial phosphorus–fluorine[12] coupling constant of 950–990 cps and the normal axial coupling constant found near 800 cps. Thus it is reasonable to expect that a rapid equilibration of the phosphorus–fluorine bonding orbitals is occurring. The figures above are similar to that reported at 25° for the aliphatic cyclic compound $(CH_2)_4PF_3$, 915 cps.[13] In this instance rapid equilibration of the bonding orbitals was postulated to explain the fluorine equivalence.

The ^{19}F spectra of $2,6\text{-}Et_2C_6H_3NHPF_4$ contained three doublets, one twice as intense as the other two. The more intense set was spaced at 940 cps while the weaker doublets were spaced at 730 cps. The more intense set at 940 cps indicates two equivalent equatorial fluorine atoms. The weaker doublets at 730 cps indicate that the axial fluorines are not equivalent. It may be that the axial fluorine atoms are rendered slightly nonequivalent by the geometry of the 2,6-diethylanilino group attached to the phosphorus atom since rotation may be somewhat hindered. A satisfactory spectrum of $2,6\text{-}Me_2C_6H_3NHPF_4$ was not obtained because of insufficient solubility at room temperature.

Infrared Spectra.—The spectra were run in halocarbon from 5000 to 1330 cm^{-1} and from 1330 to 625 cm^{-1} in Nujol for crystalline products and on neat film for liquid products on a Beckman IR-5A calibrated with polystyrene film.

The varying products, *i.e.*, $R_3NH^+PF_6^-$, RNH_2–PF_5, $RNHPF_4$, and $(RNPF_3)_2$, reported here have infrared spectra which are quite useful in characterizing the products formed. The most significant bands were those in the NH and P–F regions as discussed for each class of compound in the following paragraphs.

The major infrared bands of the cyclic dimer are shown in Table V. The most important indication of dehydrofluorination to the cyclic dimer was the complete absence of bands in the 3200-cm^{-1} region which would indicate presence of NH bonds. All the cyclic dimers contained four very strong absorptions, two

(11) L. G. Hoard and R. A. Jacobson, *J. Chem. Soc., Ser. A*, 1203 (1966).
(12) R. Schmutzler, *ibid.*, 4551 (1964).
(13) E. L. Mutterties, W. Mahler, and R. Schmutzler, *Inorg. Chem.*, **2**, 613 (1963).

TABLE V

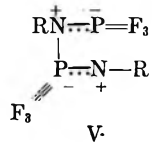
MAJOR INFRARED BANDS[a] OF CYCLIC DIMERS $(RNPF_3)_2$

R					
Phenyl	2,4-Dimethylphenyl	2,6-Dimethylphenyl	2,6-Diethylphenyl	*n*-Propyl	*t*-Butyl
1590 m					
1490 ms	1500 ms	1470 ms	1460 m		
1280 s	1282 d, s	1270 ms	1265 ms	1282 m	1245 ms
	1235 ms	1230 ms	1220 ms	1220 s	1190 ms
				1175 ms	
	1136 ms	1112 ms	1115 ms	1160 m	1136 m
1080 s	1070 ms	1071 ms	1075 ms	1050 m	1052 m
		1040 ms	1030 m		
962 s	967 s	978 m	975 m	975 s	941 s
911 s	919 s	932 s	942 s	922 s	917 s
			928 s	876 ms	
826 s	824 s	830 ms	830 s	841 s	840 ms
793 s	775 s	792 s	800 s	799 s	807 s
		781 s	777 s	781 ms	
754 m		732 m	747 ms		736 ms
693 m	722 m	718 m	713 ms		

[a] Absorptions are given in cm^{-1}; carbon–hydrogen absorptions at 2800 and 1420 cm^{-1} have been omitted.

between 980 and 910 cm^{-1} and two between 850 and 790 cm^{-1}. The absorptions are undoubtedly associated with the phosphorus–fluorine and perhaps the phosphorus–nitrogen bonds. Detailed analysis of the spectra is not attempted here, but it should be noted that the highest of these bands, near 980 cm^{-1}, is at somewhat higher frequency than the upper limit of 940 cm^{-1} reported for the phosphorus–fluorine absorptions in a large number of pentacovalent phosphorus fluorine compounds.[14] These authors did not include the pentacovalent but tetracoordinated phosphonitrilic fluorides which have phosphorus–fluorine absorptions at 980 cm^{-1}.[15] If the cyclic dimers follow the absorption patterns of other pentacovalent, pentacoordinated phosphorus compounds, the phosphorus–nitrogen ring frequency is probably near 980 cm^{-1}. However, the infrared spectrum of $(MeNPCl_3)_2$ shows only a single strong band, previously suggested[16] to be the phosphorus–nitrogen ring vibration, located at 847 cm^{-1}, in the region from 980 to 790 cm^{-1}. Thus one might assign the phosphorus–nitrogen ring frequency in the compounds reported here to the band found near 830 cm^{-1}. Since this frequency is in the absorption region of phosphorus–fluorine bonds, extensive coupling would be expected; so it may not be meaningful to consider separate phosphorus–nitrogen and fluorine–phosphorus absorptions for this system.

Assignment of the ring phosphorus–nitrogen vibrations to strong bands appearing at somewhat higher frequencies is possible, if one would accept the premise that the ring bond strength is considerably influenced by the ability of the nitrogen atom to donate its electrons to the ring. This premise would seem to be established[17] by the effect of amine base strength on dimer formation and stability and reported delocalization of the nitrogen lone pair for $(Cl_3PNMe)_2$,[16] but is contradictory to findings that there is no delocalization of the nitrogen atom lone pair for $(F_3PNMe)_2$.[8] From the effect of base strength on dimer stability we would assign the phosphorus–nitrogen ring vibrations to a very strong absorption at 1220 for N-propyl, to 1135 for N-*t*-butyl whose ring strength might be weakened by steric factors, and to bands in the 1110–1075-cm^{-1} region for the N-aromatic derivatives where the nitrogen atom should be much less basic. These latter assignments are somewhat intermediate between absorptions expected for complete double-bond character as in the phosphonitrilic fluorides[18] which have ring frequencies at 1287–1439 cm^{-1} and that expected for phosphorus–nitrogen single bonds[19] and are thus reasonable since one might expect significant contributions from structures such as V. In addition to the bands mentioned above, a strong



V

doublet at 1230 and 1270 cm^{-1} was found in the case when R was 2,4-dimethylphenyl, 2,6-dimethylphenyl, and 2,6-diethylphenyl.

The aminophosphorus tetrafluorides were readily characterized by their lack of absorption in the NH_2 region near 1600, coupled with a sharp absorption near 3350 cm^{-1}, characteristic of a single N–H bond. The 3350-cm^{-1} band in the 2,4-dimethylphenyl and 2,6-diethylphenyl derivatives appeared as a very sharp doublet (readily distinguishable from the much broader NH_2 doublet in the same region). Since the compounds were indicated to be pure by vpc, the splitting must be caused by positional isomerization of the NH group with respect to the remainder of the molecule, which is caused perhaps by restriction of the phenyl group rotation by its *ortho* substituent. The aromatic aminophosphorus tetrafluorides had absorption bands in common at 1260, 1040, and 940 and a very intense band at 860 cm^{-1}. The isopropyl derivative had bands at 1110 and 940 and a very strong band at 860 cm^{-1}. The 1260-cm^{-1} band is probably derived from phenyl nitrogen stretching vibrations, whereas bands at 940 cm^{-1} and 860 are derived from phosphorus fluorine vibrations. However, the band at 1040 cm^{-1} (or 1110 cm^{-1} for the isopropyl derivative) seems to be of too high frequency to be derived from the phosphorus–fluorine vibrations and would most likely be assigned to the nitrogen–phosphorus vibration. Assignment of the band to this bond indicates considerable double-bond character to the nitrogen phosphorus bond. The double-bond character would be sensitive to the basicity of the amine, since more strongly basic amines should increase the double-bond character of the nitrogen–phosphorus bond. Thus the absorption frequency changes from 1040 (for aromatic compounds) to 1110 cm^{-1} (for an aliphatic product). The principal absorption bands are shown in Table VI.

The infrared spectra of the amine hexafluorophosphate salts had several distinctive characteristics. The most important band was a very strong absorption at 860–810 cm^{-1} which, upon sample dilution, gave a

(14) R. A. Chittendon and L. C. Thomas, *Spectrochim. Acta*, **21**, 861 (1965).

(15) A. C. Chapman and N. L. Paddock, *J. Chem. Soc.*, 635 (1962).

(16) A. C. Chapman, W. S. Holmes, N. L. Paddock, and H. T. Searle, *ibid.*, 1825 (1961).

(17) I. N. Zhmurova and B. S. Drach, *Zh. Obshch. Khim.*, **39**, 1441 (1964).

(18) A. C. Chapman, N. L. Paddock, D. H. Paine, H. T. Searle, and D. R. Smith, *J. Chem. Soc.*, 3608 (1960).

(19) A. B. Burg and J. Heners, *J. Amer. Chem. Soc.*, **87**, 3092 (1965).

TABLE VI

MAJOR INFRARED BANDS[a] OF AMINOPHOSPHORUS TETRAFLUORIDE

Amine			
2,6-Diethylaniline	2,6-Dimethylaniline	2,4-Dimethylaniline	Isopropylamine
3400 m	3350 m	3400 m	3420 m
3360 m		3350 m	
1270 m	1265 m	1265 m	1178 s
1205 m	1218 ms	1225 m	1160 ms
1115 m	1101 s	1130 m	1136 m
1052 s	1042 s	1043 vs	1108 s
1032 ms	1028 s		
941 s	948 s	941 vs	940 vs
857 vs	863 vs	860 vs	845 vs
820 ms	810 s	845 s	
801 m	780 s	782 m	794 m
760 m			
749 m			

[a] Absorptions are given in cm^{-1}; carbon–hydrogen bands at 2800 and 1420 cm^{-1} have been omitted.

single maximum between 840 and 828 cm^{-1}. Although the other products reported here also had absorptions in this region, these were less intense and were composed of several bands. Also present was a weaker, but still strong band at 741–747 cm^{-1}. Each of these bands has been reported[20] to be characteristic of the PF_6^- anion. The primary amine salts had absorptions at 1600 cm^{-1} characteristic of NH_3 groups and a strong absorption in the nonbonded N–H stretching region at 3200 cm^{-1}, which could not be resolved by sample dilution. The salts had none of the bonded N–H absorptions from 2500 to 2800 cm^{-1} usually present in amine salts, since the large hexafluorophosphate anion is capable of only weak coordination to the amine.

The primary amine phosphorus pentafluoride adducts were readily distinguished from the hexafluorophosphate salts at two points in the spectra. The N–H absorption at 3200 cm^{-1} could be resolved into a doublet for the adduct, but not for the salt. Again although the adducts had strong absorptions in the 830–900-cm^{-1} region, as did the salt, these absorptions gave several peaks when the sample was diluted. The spectra of the amine salts and adducts are listed in Tables VII and VIII.

Experimental Section

Reagents.—Phosphorus pentafluoride was obtained during the early stage of this research by the decomposition at 160–180° of Phosfluorogen (*p*-chlorophenyldiazonium hexafluorophosphate) from Ozark-Mahoning Co. More recently it was obtained in cylinders from Ozark-Mahoning Co. or the Matheson Co. Diisopropylethylamine was obtained from Aldrich Chemical Co. Depending upon volatility amines were distilled from potassium hydroxide pellets onto calcium hydride either in an atmosphere of N_2 or at reduced pressures. Solvents such as benzene or heptane were *in situ* by azeotroping them in the reaction flask, then cooling under N_2.

Procedure.—Standard laboratory three-necked flasks and Trubore stirrers were used. The reaction vessel was thoroughly flushed with dry N_2 and vented only to dry N_2. During phosphorus pentafluoride addition the flask was vented to a N_2 stream through a mineral oil bubbler which served to indicate phosphorus pentafluoride absorption by the reaction mixture. All filtrations were done in sintered-glass pressure funnels under N_2.

In a typical experiment 50 ml of benzene was distilled from 300 ml of benzene contained in a 500-ml flask. After the flask and contents had cooled the amine was transferred to the flask by pipetting under the benzene in the N_2-flushed flask. The flask contents were then stirred rapidly while phosphorus pentafluoride was admitted at a rate that gave slow or no gas evolution at the exit bubbler. It was necessary to cool the flask at this time since the reaction is quite rapid and exothermic. After phosphorus pentafluoride addition was completed the flask was warmed to reaction temperature (except in a few instances where the mixture was filtered cold). After reaction was completed the system was flushed with N_2 to remove excess phosphorus pentafluoride and the reaction mixture was filtered. Generally, the solvent-insoluble solids contained salt or adduct while the filtrate contained dehydrofluorination products and/or excess amine.

TABLE VII

MAJOR INFRARED BANDS[a] OF PHOSPHORUS PENTAFLUORIDE–AMINE ADDUCTS

Aniline	2,6-Dimethylaniline	*n*-Propylamine
3250 d, m	3270 d, m	3290 s
3110 w		2525 s
1600 w	1505 m	
1575 m	1560 m	1640 s
		1600 s
1475 mw		1510 m
1495 mw		
1320 s		
	1295 s	
1080 m	1173 m	1190 m
920 s	1098 m	1050 m
892 vs	1037 m	1018 m
848 s	939 s	862 s, sh
835 s	892 vs	840 vs
812 s	872 vs	748 s
798 vs	820 vs	
766 m	770 m	
	715 m	
692 s		

[a] Absorptions are given in cm^{-1}; carbon–hydrogen bands at 2800 and 1420 cm^{-1} have been omitted.

Reaction of Aniline and Phosphorus Pentafluoride. A. In Absence of Tertiary Amine.—Aniline was treated with phosphorus pentafluoride under different conditions as listed in Table IX. It is apparent from Table IX that the initial adduct is reactive toward either aniline or phosphorus pentafluoride.

A sample of the cyclic dimer 2,2,2,4,4,4-hexafluoro-2,2,4,4-tetrahydro-1,3-diphenyl-1,3,2-4-diazadiphosphetidine was analyzed.

Anal. Calcd. for $C_{12}H_{10}N_2P_2F_6$: C, 40.25; H, 2.78; N, 7.82; P, 17.30; F, 31.83. Found: C, 40.04; H, 2.89; N, 7.73; P, 17.46; F, 31.66.

The adduct was also analyzed.

Anal. Calcd. for $C_6H_7NPF_5$: N, 6.57; P, 13.9; F, 43.4. Found: N, 6.39; P, 14.1; F, 43.4.

Analyses[21] of the anilinium hexafluorophosphate for the hexafluorophosphate anion indicated 60.77% PF_6^- (theory, 60.63%).

The stability of the adduct depended upon its method of preparation and purity. Adduct contaminated with salt was recovered from refluxing benzene. However, adduct prepared with a deficiency or equal quantity of phosphorus pentafluoride decomposed according to eq 4 in the text when refluxed in benzene or heated at reduced pressure. (This conclusion is tentative since $PhNHPF_4$ was inferred from the spectra and volatility but not analyzed; salt $PhNH_3^+PF_6^-$ was isolated and analyzed.) Adduct prepared in excess phosphorus pentafluoride decomposed to salt and cyclic dimer when refluxed in benzene, heated in N_2 at 165°, or heated at reduced pressure to 120°. Apparently small quantities of residual aniline (or phosphorus pentafluoride to which the analytical methods and spectra are not sensitive) changes the stability and mode of decomposition of the adduct.

Refluxing 0.35 g (0.001 mol) of $(PhNPF_3)_2$ with 0.1 g (0.00107 mol) of aniline in 25 ml of benzene for 2 hr left 0.45 g of benzene-soluble solids containing none of the starting cyclic dimer.

B. In Presence of Triethylamine.—Aniline (8.4 g, 0.07 mol) and triethylamine (18.2 g, 0.181 mol) in 250 ml of benzene were

(20) R. D. Peacock and D. W. A. Sharp, *J. Chem. Soc.*, 2762 (1959).

(21) H. E. Affsprung and V. S. Archer, *Anal. Chem.*, **35**, 976 (1963).

TABLE VIII

MAJOR INFRARED BANDS[a] OF AMINE HEXAFLUOROPHOSPHATE SALTS

n-Propyl-amine	Isopropyl-amine	*t*-Butyl-amine	Triethyl-amine	Aniline	2,4-Dimethyl-aniline	2,6-Dimethyl-aniline	2,6-Diethyl-aniline
3270 ms	3270 ms	3250 m	3200 s	3210 s	3200 s	3210 s	3200 s
1600 ms	1605 s	1610 m		1580 s	1590 m	1640 m	1620 ms
				1515 m		1590 m	1590 ms
				1492 m	1493 s	1490 s	1497 s
		1300 s					
	1210 s	1215 ms	1190 mw				
	1160 m	1140 ms	1168 m				
	1135 m		1062 ms	1088 m	1040 m	1100 m	1100 m
1009 m			1030 s				990 m
985 m	985 m					862 s	862 s
822 vs	835 vs	832 vs	840 vs	828 vs	833 vs	830 s	830 vs
753 m	740 m	740 m	740 m	740 m	740 m	770 m	742 m
				685 m		740 m	

[a] Absorptions are given in cm^{-1}; carbon–hydrogen bands at 2800 and 1420 cm^{-1} have been omitted.

TABLE IX

REACTION OF ANILINE WITH PHOSPHORUS PENTAFLUORIDE

Aniline, g	PF_5	Time, min (temperature, °C)	Subsequent reaction time, min (temperature, °C)	Products
25.6	Deficient	15 (0)	None	Adduct 45.6 g, 100%; recovered aniline 6.0 g
10.2	Equal	10 (0–5)	10 (5)	Adduct 20.4 g, 90%; 1 g of others
33.6	Equal	30 (0)	8 hr (25)	Adduct 64.7 g, 82%; 6.3 g of oils, aniline + others
1.02	Equal	60 (5)	None	Adduct 2.3 g, 100%
10.2	Deficient	2.5 hr (25)	8 hr (25)	5.8 g of $PhNH_3^+PF_6^-$, 11.2 g of soluble products, possibly $PhNH_3^+PF_5PhNH$ and $(PhNH)_2PF_3$
1.02	Equal	3 (25)	None	Adduct 2.2 g, 92%
5.1	Excess	10 (0)	10 (0)	Adduct 85%; decomposed in 2 days to dimer and salt
10.2	Excess	30 (25)	8 hr (25)	$PhNH_3^+PF_6$ 15.2 g, 86%; cyclic dimer 5.6 g, 86%

treated with phosphorus pentafluoride at 25° giving 42.2 g (0.172 mol, 95% yield) of insoluble white solids, mp 80°, triethylammonium hexafluorophosphate, and 14.4 g of $(PhNPF_3)_n$ dehydrofluorination product. The latter was sublimed to give 7.8 g (0.0218 mol, 48.5% yield) of cyclic dimer. The remaining product (6.6 g) could not be distilled at 0.5 mm to 225°. Ebullioscopic molecular weight of the residue was 703. The infrared spectrum of the residue indicated weak NH and PF_4 bands, perhaps as end groups.

Analysis of triethylammonium hexafluorophosphate for the hexafluorophosphate anion indicated 58.50% PF_6^- (theory, 58.87%).

Reaction of the Adduct of Aniline and Phosphorus Pentafluoride with Diisopropylethylamine Boron Trifluoride.—A stirred solution of 38.6 g (0.196 mol) of diisopropylethylamine boron trifluoride in 250 ml of benzene was allowed to react at 25–35° with 20.0 g (0.0197 mol) of aniline phosphorus pentafluoride from a solids addition funnel. Recovered were 43.4 g of insoluble solids, mainly diisopropylethylammonium tetrafluoroborate[22] (0.200 mol, 100+% yield) and 11.9 g of crude dehydrofluorination product $(PhNPF_3)_n$. Purification gave 4.5 g (0.0126 mol, 25% yield) of cyclic dimer. The remaining product was higher molecular weight oils.

Reaction of 2,4-Dimethylaniline and Phosphorus Pentafluoride. A. In Absence of Tertiary Amine.—Reaction of 9.78 g (0.0806 mol) of 2,4-dimethylaniline with excess phosphorus pentafluoride in 250 ml of benzene followed by 4 hr of refluxing gave 10.4 g (0.0389 mol, 96.7% yield) of benzene-insoluble 2,4-dimethylanilinium hexafluorophosphate and 8.7 g (0.0384 mol, 95.5% yield) of crude 2,4-dimethylanilinophosphorus tetrafluoride. Distillation of the crude material at 60° (5 mm) gave 5.0 g (0.022 mol, 55% yield) of 2,4-dimethylanilinophosphorus tetrafluoride.

Anal. Calcd for $C_8H_{10}NPF_4$: N, 6.17; P, 13.64; F, 33.46. Found: N, 6.24; P, 13.74; F, 32.75.

The distillation residue contained 2,4-dimethylanilinium hexafluorophosphate, cyclic dimer described below, and an oil, bp 140° (0.1 mm). The oil was not characterized but had an infrared spectrum consistent with the structure $(ArNH)_2PF_3$.

(22) J. J. Harris, *Inorg. Chem.*, **5**, 1627 (1966).

Analysis of 2,4-dimethylanilinium hexafluorophosphate for the hexafluorophosphate group indicated 54.74% PF_6^- (theory, 54.26%).

B. In Presence of Triethylamine.—Reaction of 10.9 g (0.09 mol) of 2,4-dimethylaniline and 18.2 g (0.181 mol) of triethylamine in 125 ml of benzene with phosphorus pentafluoride at 25° gave 42.4 g (0.172 mol, 95% yield) of triethylammonium hexafluorophosphate and 20.0 g of benzene-soluble liquid–solids. Heating the latter at 0.5 mm caused distillation of a small quantity of 2,4-dimethylanilinophosphorus tetrafluoride (see above) at 42–44°. At 140–150° there was sublimed 15.8 g (0.0382 mol, 85% yield) of 2,2,2,4,4,4-hexafluoro-2,2,4,4-tetrahydro-1,3-bis(2,4-dimethylphenyl)-1,3,2,4-diazadiphosphetidine.

Anal. Calcd for $C_{16}H_{18}N_2P_2F_6$: C, 46.39; H, 4.38; N, 6.76; P, 14.96; F, 27.52; mol wt, 414.3. Found: C, 46.38; H, 4.56; N, 6.99; P, 14.94; F, 27.48; mol wt, 413 (ebullioscopic).

Reaction of 2,6-Dimethylaniline with Phosphorus Pentafluoride. A. In Absence of Tertiary Amine.—A solution of 9.8 g (0.081 mol) of 2,6-dimethylaniline in 150 ml of benzene was allowed to react at 25° with phosphorus pentafluoride, then refluxed for 5 hr. Recovered were 10.8 g (0.0405 mol, 100% yield) of benzene-insoluble 2,6-dimethylanilinium hexafluorophosphate, subliming unchanged at 160–180° (0.5 mm), and 8.9 g (0.0392 mol, 97% yield) of 2,6-dimethylanilinophosphorus tetrafluoride. There was no evidence for formation of the completely dehyrofluorinated cyclic dimer.

Anal. Calcd for $C_8H_{10}NPF_4$: C, 42.30; H, 4.44; N, 6.17; P, 16.64; F, 33.46. Found: C, 42.75; H, 4.61; N, 6.15; P, 16.35; F, 33.47.

Analysis of 2,6-dimethylanilinium hexafluorophosphate for the hexafluorophosphate anion indicated 54.42% PF_6^- (theory, 54.26%).

Stopping the reaction of 9.8 g (0.081 mol) of 2,6-dimethylaniline in 125 ml of benzene with phosphorus pentafluoride while absorption was rapid and filtering immediately gave 5.7 g (0.0207 mol, 26.6% yield) of solid 2,6-dimethylaniline phosphorus pentafluoride adduct. The filtrate in which solids had formed soon after filtration gave, after standing 6 hr, 6.1 g (0.0228 mol, 28% yield) of 2,6-dimethylanilinium hexafluorophosphate and 5.8 g (0.0255 mol, 31.5% yield) of crude 2,6-dimethylanilinophosphorus tetrafluoride. Apparently the adduct is somewhat

soluble in benzene and disproportionates upon standing. Repeating the above reaction in heptane at 15° gave 7.0 g (0.0254 mol, 31%) of heptane-insoluble adduct. The filtrate contained only 6.73 g (0.0556 mol) of unreacted 2,6-dimethylaniline. The adduct, being heptane insoluble, precipitates immediately and further reaction was stopped.

2. **In Presence of Triethylamine.**—Addition of phosphorus pentafluoride to 14.1 g (0.121 mol) of 2,6-dimethylaniline and 26.4 g (0.26 mol) of triethylamine in 250 ml of benzene until its absorption was complete at room temperature, followed by refluxing for 3 hr, gave a tan oil and a clear supernatant liquid. The reaction mixture, cooled without stirring, formed a solid cake from the bottom oil and 15.2 g of long white needles in the top layer. Refluxing the oil with fresh benzene gave recovery of 6.5 g of additional product for a total recovery of 21.7 g (0.0525 mol, 86.5% yield) of 2,2,2,4,4,4-hexafluoro-2,2,4,4-tetrahydro-1,3-bis(2,6-dimethylphenyl)-1,3,2,4-diazadiphosphetidine.

Anal. Calcd for $C_{16}H_{18}N_2P_2F_6$: C, 46.39; H, 4.38; N, 6.76; P, 14.95; F, 27.52; mol wt, 414.3. Found: C, 46.97; H, 4.61; N, 6.47; P, 15.07; F, 27.03; mol wt, 398 (ebullioscopic).

The dimer sublimed leaving no appreciable residue; hence significant quantities of higher molecular weight products were absent. The solid formed when the bottom layer oil from the reaction was cooled to room temperature gave 62.3 g (0.253 mol, 100% yield based on 2,6-dimethylaniline) of triethylammonium hexafluorophosphate.

Reaction of 2,6-Diethylaniline with Phosphorus Pentafluoride. A. In Absence of Tertiary Amine.—Phosphorus pentafluoride was added at 25° to 9.5 g (0.0637 mol) of 2,6-diethylaniline in 250 ml of benzene until it s absorption was complete, then the mixture was refluxed 4 hr. Recovered from the filtrate was 7.9 g (0.031 mol, 97% yield) of 2,6-diethylanilinophosphorus tetrafluoride.

Anal. Calcd for $C_{12}H_{14}NPF_4$: C, 47.06; H, 5.53; N, 5.49; P, 12.14; F, 29.78. Found: C, 47.06; H, 5.83; N, 5.81; P, 11.86; F, 30.09.

Also formed was 9.4 g (0.0318 mol, 100% yield) of white benzene-insoluble solids (2,6-diethylanilinium hexafluorophosphate). Analysis of the salt for the hexafluorophosphate anion indicated 49.45% PF_6^- (theory, 49.11%).

Reacting 2,6-diethylaniline at 10° with a deficiency of phosphorus pentafluoride in either benzene or heptane for 10 min followed by immediate filtration gave the same products as above. The rapid formation of solid 2,6-diethylanilinium hexafluorophosphate in the filtrate from the reaction indicated that a soluble adduct may have formed but rapidly disproportionated.

B. In Presence of Triethylamine.—Treating 17.0 g (0.114 mol) of 2,6-diethylaniline and 25.3 g (0.25 mol) of triethylamine in 250 ml of benzene with phosphorus pentafluoride at room temperature followed by 6 hr of reflux gave a two-layer system. Removal of volatiles from the top layer left 25.4 g (0.054 mol, 94% yield) of yellow crystals, crude 2,2,2,4,4,4-hexafluoro-2,2,4,4-tetrahydro-1,3-bis(2,6-diethylphenyl)-1,3,2,4-diazadiphosphetidine. These formed white crystals when sublimed at 120–140° (0.025 mm) or recrystallized from benzene.

Anal. Calcd for $C_{20}H_{26}N_2P_2F_6$: C, 51.07; H, 5.57; N, 5.96; P, 13.17; F, 24.24; mol wt, 470.9. Found: C, 51.55; H, 5.60; N, 6.00; P, 13.29; F, 24.42; mol wt, 466 (ebullioscopic).

The bottom layer cake was mainly triethylammonium hexafluorophosphate containing cyclic dimer and a small amount of unreacted 2,6-diethylaniline.

No reaction occurred when 1.65 g (0.0035 mol) of the cyclic dimer $(2,6\text{-}Et_2C_6H_6NPF_3)_2$ was refluxed with 0.45 g (0.003 mol) of 2,6-diethylaniline for 4 hr in benzene.

Reaction of Phosphorus Pentafluoride with *o*-Phenylenediamine. A. In Absence of Triethylamine.—Phosphorus pentafluoride, when added to 25 g (0.232 mol) of *o*-phenylenediamine in 125 ml of chlorobenzene formed 53.6 g (0.23 mol) of *o*-phenyl enediamine phosphorus pentafluoride. A 1:1 adduct was indicated by reaction stoichiometry and analysis.

Anal. Calcd for $C_6H_8N_2PF_5$: C, 30.90; H, 3.46; N, 12.01; P, 12.90; F, 40.73. Found: C, 29.58; H, 3.73; N, 11.30; P, 12.76; F, 38.73.

These figures, although somewhat unsatisfactory in regard to product purity, definitely indicate the product to be a 1:1 adduct.

B. In Presence of Triethylamine.—Reagents were used in the proper stoichiometry to give 1,3-dihydro-2,2,2-trifluoro-1,3,2-benzodiazaphosphate.

A mixture of 50 g (0.463 mol) of *o*-phenylenediamine and 96.3 g (0.926 mol) of triethylamine in 250 ml of chlorobenzene was treated with 185 g (1.47 mol) of phosphorus pentafluoride. As the reaction progressed solids formed and redissolved, immiscible layers formed, then solids reappeared. The solids finally formed contained all but traces of the reaction products. By infrared spectra they contained triethylammonium hexafluorophosphate and aromatic species. Separation of the aromatic product was not achieved in chloroform, benzene, dioxane, diethyl ether, triethylamine, or tetrahydrofuran used separately or in combinations. Only a fraction sublimed to 210° (0.5 mm) and the sublimate did not show separation into definite products. Repeating the experiment using sufficient triethylamine to form a benzodiazaphosphate as the repeating unit of polymer IV gave similar results.

Reaction of Phosphorus Pentafluoride with *n*-Propylamine. A. In Absence of Tertiary Amine.—A mixture of 7.3 g (0.122 mol) of *n*-propylamine in 125 ml of benzene was treated with phosphorus pentafluoride at 25°, then refluxed 6 hr. Filtering the mixture gave 13.4 g (0.065 mol) of *n*-propylammonium hexafluorophosphate. Removing benzene from the filtrate left a liquid product distilling at 40–100° (20 mm) to give a two-layer distillate and 0.7 g of still residue. The top layer contained 1.0 g (0.0035 mol, 17% yield) of 2,2,2,4,4,4-hexafluoro-2,2,4,4-tetrahydro-1,3-di-*n*-propyl-1,3,2,4-diazadiphosphetidine.

Anal. Calcd for $C_6H_{14}N_2P_2F_6$: C, 24.84; H, 4.86; N, 9.66; P, 21.35; F, 39.29. Found: C, 25.00; H, 5.21; N, 9.75; P, 21.29; F, 39.19.

The bottom layer was an oil containing NH and PF_4 or PF_5 infrared bands, perhaps from linear species containing PrNH or PF_4 end groups.

A similar reaction of 3.6 g (0.061 mol) of *n*-propylamine in 100 ml of heptane at 10° with a deficiency of phosphorus pentafluoride gave 5.0 g of very hygroscopic heptane-insoluble solids. The filtrate yielded 2.0 g of liquid product. These solids, when heated at 1 mm of pressure, were molten at 80°, gave 0.5 g of liquid distillate at 90–115°, and resolidified at 110°. The solid product was *n*-propylammonium hexafluorophosphate. The distillate, not identified, was similar, by infrared analysis, to the liquid product from the filtrate, and distilled at 25–75° (1 mm). Cyclic dimer was not present in the liquid product from the reaction nor in the liquid distillate from pyrolysis of the solids. The original insoluble solids presumably contained adduct which decomposed when heated to salt and other products.

B. In Presence of Triethylamine.—A mixture of 7.18 g g (0.121 mol) of *n*-propylamine and 25.5 g (0.25 mol) of triethylamine in 125 ml of benzene was treated at 0° with phosphorus pentafluoride, then allowed to warm to room temperature. Filtering the mixture followed by removal of benzene from each fraction gave 60.0 g (0.243 mol, 97% yield) of triethylammonium hexafluorophosphate and 12.0 g of benzene-soluble liquid. The benzene-soluble liquids formed a two-layer system. Distillation gave 6.3 g (0.0217 mol, 36% yield) of cyclic dimer. Further distillation gave 2.0 g of liquid, bp 90–105° (0.8 mm), free from infrared bands in the N–H regions but showing absorption at 1620 cm^{-1} indicating a C=C or C=N group. Dehydrofluorination may have occurred at the aliphatic carbon atom. Analysis indicated a ratio of $(PrN)_3P_2F_4$.

Reaction of Phosphorus Pentafluoride with Isopropylamine.—A soluion of 17.3 g (0.293 mol) of isopropylamine in 125 ml of benzene was treated at 25° with phosphorus pentafluoride until its absorption was complete. Filtering the mixture gave 23.7 g of wet filter cake indicated by infrared analysis to contain isopropylammonium hexafluorophosphate and other products. The solids were heated to 190° (0.5 mm), then slurried in benzene, filtered, and dried to obtain an analytical sample of the salt. Analysis for the hexafluorophosphate anion indicated 70.74% PF_6^- (theory, 70.69). Removal of solvent from the two-layer filtrate left 16 g of viscous oil which consisted of a mixture of products (not identified). Similar results were obtained when addition of phosphorus pentafluoride was stopped before its absorption was completed. In neither instance were there indications of formation of the adduct or cyclic dimer. The infrared spectrum of the oil was consistent with a formula of the type $RNH_3^+PF_5NHR^-$ since it contained absorptions of the $-NH_3^+$ group, NH group, and absorptions intermediate between PF_6^- and $RNH_2 \cdot PF_5$.

Reaction of 0.7 g of isopropylamine in heptane at −20° until absorption was complete gave 1.4 g of heptane insolubles indicated by infrared to be impure adduct. When heated to 100° the adduct formed *i*-$PrNH_3^+PF_6^-$ and other products.

Reaction of Phosphorus Pentafluoride with *t*-Butylamine in Presence of Triethylamine.—A mixture of 6.98 g (0.0955 mol) of *t*-butylamine and 19.4 g (0.181 mol) of triethylamine in 250 ml of benzene was treated with phosphorus pentafluoride at 10° until absorption was complete, then refluxed 5 hr. Filtering the mixture gave 45.9 g (0.186 mol, 97% yield) of insoluble triethylammonium hexafluorophosphate, whereas removal of volatiles from the filtrate at 10 mm left 8.8 g of solids. These were sublimed to give 6.0 g (0.0188 mol, 40% yield) of 2,2,2,4,4,4-hexafluoro-2,2,4,4-tetrahydro-1,3-di-*t*-butyl-1,3,2,4-diazadiphosphetidine.

Anal. Calcd for $C_8H_{18}N_2P_2F_6$: N, 8.81; P, 19.47; F, 35.83. Found: N, 8.33; P, 19.56; F, 35.58.

Dehydrofluorination of the Adduct of Ammonia and Phosphorus Pentafluoride.—The adduct of ammonia and phosphorus pentafluoride[23] was prepared by several procedures: (1) the addition of phosphorus pentafluoride to ammonia dissolved in ethyl ether at −78° or at 25°, (2) addition of phosphorus pentafluoride to liquid ammonia at −78° until its absorption was complete, and (3) alternate addition at room temperature of ammonia and phosphorus pentafluoride to an evacuated flask until a desired quantity had formed. Finally the flask was kept in an atmosphere of phosphorus pentafluoride for several hours to ensure that no $(NH_3)_2PF_5$ formed.[23] Procedure 3 gave material with the "cleanest" spectrum. *Warning:* The powdery adduct, even when handled in the hood, at times caused a choking feeling and tightness around the throat. This feeling lasted from 1–8 hr in two workers in the vicinity. Due caution in handling is advised.

The adduct formed above was treated with quantities of triethylamine or diisopropylethylamine–phosphorus pentafluoride stoichiometrically or in slight excess of that required for dehydrofluorination to phosphonitrilic fluorides using benzene, diethyl ether, tetrahydrofuran, pyridine, or mixtures as solvent at room to reflux temperatures. Insolubility of the adduct was a problem when benzene was used for the solvent but small yields of phosphonitrilic fluorides (trimer, tetramer, and pentamer) were found. No phosphonitrilic fluorides were formed when pyridine, diethyl ether, or tetrahydrofuran was the solvent. The principal product with each solvent was an oil not readily separated from the by-product tertiary amine hexafluorophosphate salt. Although some concentration of the oil was obtained by centrifugation, analysis was not meaningful. The oil had very strong infrared bands at 1280–1250 and 910–930 and weaker bands at 3350 cm^{-1}. Possibly polymeric products of the type $(-NH-PF_4-)_n$ were formed The dehydrofluorination of ammonia phosphorus pentafluoride is evidently quite complex. There were indications of other types of products. For example, distillation of the solvent in one instance gave a fraction with a strong phosphine odor and a strong infrared band at 2400 cm^{-1}, characteristic of phosphines.

Analyses were from these laboratories, Galbraith Laboratories, and Schwarzkopf Microanalytical Laboratories. Nmr analyses were made by Varian Associates.

Registry No.—**A1,** 15199-01-6; **A2,** 15893-20-6; **A3,** 15893-21-7; **A4,** 15893-23-9; **A5,** 15893-24-0; **A6,** 15893-22-8; **B1,** 15893-25-1; **B2,** 15893-26-2; **B3,** 15893-27-3; **B4,** 15893-28-4; **C1** (adduct), 15261-57-1; **C3** (adduct), 15893-30-8; **C5** (adduct), 15893-31-9; **C6** (adduct, 15893-32-0; **C1** (salt), 12077-62-2; **C2** (salt), 12239-94-0; **C3** (salt), 12239-95-1; **C4** (salt), 12239-97-3; **C6** (salt), 12239-90-6; **C7** (salt), 12239-93-9; **C8** (salt), 12239-96-2; **C9** (salt), 12239-91-7; *t*-butylamine hexafluorophosphate, 12239-92-8; phosphorus pentafluoride, 7647-19-0; aniline, 62-53-3.

(23) S. Johnson, Ph.D. Dissertation, Purdue University, Lafayette, Ind., 1952.

Reactions of Hexafluoroacetone or *sym*-Dichlorotetrafluoroacetone with Allylic Olefins

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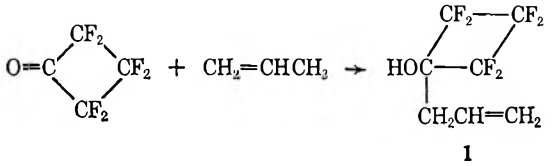
The noncatalyzed addition of highly fluorinated perhalo ketones to substituted olefins containing allylic hydrogen atoms leads to 3,4-unsaturated alcohols. The ketones act as strong electrophiles, with significant steric effects. The reaction mechanism offered involves a four-membered, cyclic dipolar intermediate, rather than a concerted mechanism previously postulated. This is based on data such as (a) interception of the intermediate by a very sensitive (difunctional) trapping agent, allyl glycidyl ether, which leads to a homopolymer of the latter, (b) formation of the adduct of β-pinene without rearrangement, and (c) an appreciable solvent effect. Implications of these findings in 1,5 hydrogen shifts, olefin additions, and concerted reactions are discussed.

The uncatalyzed addition reactions of highly fluorinated perhalo ketones to substituted olefins containing allylic hydrogen atoms generally lead to the formation of 3,4-unsaturated alcohols (2-alkenylcarbinols).

This was first demonstrated by D. C. England[1] in reaction of perfluorocyclobutanone with propylene 1.



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Davis[2] and Knunyants and Dyatkin[3,4] showed that hexafluoroacetone (HFA) or *sym*-dichlorotetrafluoroacetone (DCTFA) reacted similarly. Middleton[5] and Gambaryin, *et al.*,[6] extended the reaction to allylic compounds containing more polar groups (α-methyl styrene, methyl methacrylate, allyl methyl ether).

In this paper are reported results of uncatalyzed reactions of HFA and DCTFA with various allylic olefins which were carried out under comparable conditions. Qualitative comparisons are made of the effects of structure and solvent on reactivity and product character. Reaction mechanism is considered, as well as implications for other systems.

General Procedure

The reactions were carried out under the mildest conditions which led to appreciable conversion into

(1) D. C. England, *J. Amer. Chem. Soc.*, **83**, 2205 (1961).

(2) H. R. Davis, Abstracts, the 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961, p 25M.

(3) I. L. Knunyants and B. L. Dyatkin, *Bull. Acad. Sci. USSR, Div. Chem. Sci.* (Eng. Transl.), 329 (1962).

(4) Belgian Patent 625,425 (1962).

(5) W. J. Middleton, Central Research Department, Du Pont, unpublished work.

(6) N. P. Gambaryin, El. M. Rokhlina, and Yu. V. Zeifman, *Bull. Akad. Sci., USSR, Div. Chem. Sci.* (Eng. Trrnsl.), **8**, 1425 (1965).

TABLE I

UNCATALYZED ADDITION REACTIONS OF HEXAFLUOROACETONE OR *sym*-DICHLOROTETRAFLUOROACETONE WITH VARIOUS UNSATURATED COMPOUNDS

Fluoro ketone	Coreactant[a]	Temp, °C	Time, hr	Pressure, psi (aut., autogenous)	% conversion into adduct	Bp, °C (mm)	$n^{25}D$	Ref[b]
Hexafluoroacetone	Propylene	150[c]	2.5	440	17	97–98		A
			9		67	95–98	1.3345[d]	3, 6
	Isobutylene	RT	<24	aut.	97	113–115	1.3485[d]	3, 6
	2-Butene (*cis*- + *trans*-)	160	10	aut.	~5[e]	113		9
	Cyclohexene	160	10	aut.	~3.7[f]	73 (29)	1.3920[d]	9
	3,3-Dimethylbutene-1	150[c]	1	2480	<1			
	2,4,4-Trimethylpentene-1 (diisobutylene)	70[c]	10[g]	aut.	95	58–60 (9)	1.3768	
	Octene-1[h]	100[c]	2	aut.	75	71–73 (0.6)		M
	α-Methylstyrene	<40	4	aut.	80	110–112 (22)	1.4440	
	β-Pinene	35	2[n]	aut.	80	108–112 (24) (mp 33–34)	1.4162[i]	G
	Allyl chloride	165[c]	4	600	3	64–65 (50)	1.3700[i]	C
	2-Chloropropene-1	164[c]	4	490	10–20	53–55 (50)	1.3658[i]	B
	Allyl methyl ether	100	20	aut.	Estd 80 (to secondary products)			6
	Allyl glycidyl ether[k]	75[c]	1	40	>90 (of AGE)			
		+100	3		(to polymer)			K, L
	Methyl methacrylate[c]	150[c]	40	aut.	8–14	73 (8.5)	1.3725	5
		165	6	aut.	16	110–112 (58)	1.3725	
	Methacrylonitrile[l]	165[c]	4	640	3 (impure)	50–56 (72)	1.3739[j]	
	α-Methylvinyl methyl ether	0–35	1	aut.	>85	65–67 (36)	1.3530	J
	Styrene	130–165	6	415–450	>90 (of styrene) <1 (of HFA) (to polymer)			N
sym-Dichlorotetrafluoroacetone	2,4,4-Trimethylpentene-1	66–71	5	1 atm	50	116 (28)	1.4261	D, E F
	α-Methylstyrene	60	60	1 atm	62	86–89 (0.6)	1.492[m]	4
	β-Pinene	−70 → 0	24[n]	1 atm	62	150–155 (23)		H
	α-Pinene	100	1	1 atm	<1			I
	Allyl glycidyl ether	100	1	1 atm	<5			L
	Camphene	35	24	1 atm	<1			

[a] Equimolar ratios were used except where specified. [b] Capital letters indicate description in the Experimental Section. Numbers are literature references. [c] The reaction temperatures were held for 1 hr. If no reaction was evident, the temperature was raised by 25° and held for another hour. [d] $n^{20}D$. [e] Another 5% conversion into diadduct was obtained. [f] About 5% total conversion took place, of which 75% was monoadduct, 25% was diadduct.[g] [g] Pressure drop occurred after 0.5-hr heating. [h] Run in the presence of phenyl glycidyl ether. [i] $n^{24}D$. [j] $n^{26}D$. [k] 0.2 mol of AGE/0.1 mol of HFA. [l] Similar results were obtained with a 2:1 HFA/MAN mole ratio. [m] $n^{27}D$. [n] Heat was evolved within a few minutes.

product. That is, a 1:1 molar mixture of fluoro ketone and olefin was shaken in a sealed stainless steel tube, under nitrogen and in the presence of hydroquinone, at a given temperature for a period of time (1 hr). If no reaction occurred (no pressure drop, no exotherm), the temperature was raised 25° and the tube shaken from another hour. This procedure was repeated if necessary to a temperature of 165°. For the latter, the temperature was held for 4–6 hr, the tube cooled, and the nongaseous products characterized. Specific details are given in Table I and in the Experimental Section.

This technique gave a set of "minimum conversion temperatures," which may be considered as a relative measure of reaction rates. Although these results are qualitative, they have the advantage of being obtained under conditions reflecting kinetic control.

Results

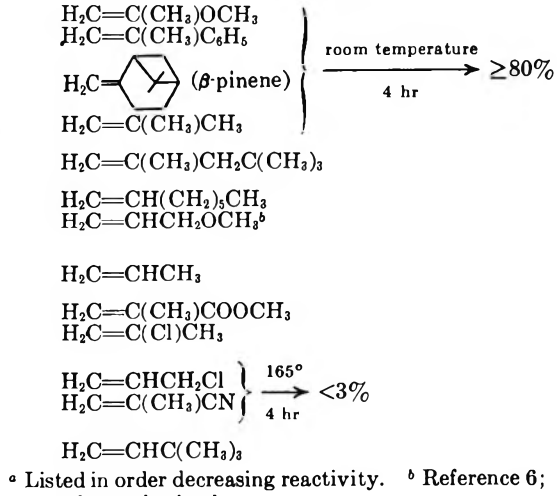
The adducts are listed in Table I. Analytical data are included in the Experimental Section.

It is evident that HFA is more reactive than DCTFA.

In Chart I, the terminal olefins are listed in order of reactivity toward adduct formation. Groupings have been made where differentiation of reactivity is not conclusive. It is apparent that electrophilic attack of the HFA or DCTFA dominates the rate-determining step of the reaction. Thus, reaction proceeded the

CHART I

RELATIVE ORDER OF REACTIVITY OF HFA WITH OLEFINS[a]



[a] Listed in order decreasing reactivity. [b] Reference 6; secondary products obtained.

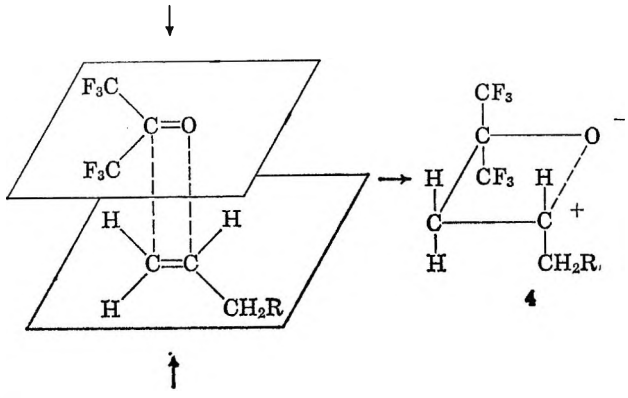


Figure 1.—Suggested approach and planar four-membered cyclic dipolar intermediate resulting from HFA and allylic olefins.

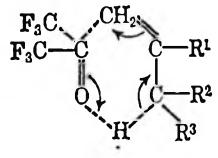
most rapidly when the olefinic double bond was asymmetrically substituted and heavily loaded with groups which were strongly electron donating. Isobutylene, α-methylvinyl methyl ether, α-methyl styrene, and β-pinene reacted rapidly (5–120 min) with HFA near room temperature or below; octene-1 or propylene reacted much more sluggishly (several hours at 100–150°); allyl chloride or methyl methylacrylate reacted still more slowly, requiring 150–165°, whereas methacrylonitrile reacted extremely slowly, even at 165–180°. 2-Chloropropene-1 was more sluggish than propylene but not so sluggish as allyl chloride.

On the other hand, reaction of HFA or DCTFA with symmetrically substituted olefins was very slow, unlike the reactivity of such electrophilic reagents as chlorine, bromine, or sulfenyl halides.[7,8] Thus *cis*- or *trans*-2-butene or cyclohexene reacted extremely slowly, even at 165–180°,[9] and α-pinene also appeared unreactive (see Table I). Therefore, steric effects in addition with HFA or DCTFA appear to be significant. The importance of steric effects is also seen by the low reactivity of DCTFA with camphene or α-pinene, and for HFA with 3,3-dimethylbutene-1.

Reaction Course and Mechanism.—In the formation of the adducts, one possibility, an insertion reaction with an allylic hydrogen, analogous to reactions of saturated aliphatic R–H with HFA in a free-radical chain reaction[10] may be ruled out, for the reaction of HFA with butene-1 led to the linear rather than to a branched adduct.[11]

Further, insertion with a vinylic hydrogen followed by a hydrogen shift seems very unlikely, based on the generally low reactivity of vinylic hydrogen and on the resistance to adduct formation of 3,3-dimethylbutene-1 or camphene.

Thus the reaction course may best be categorized (as pointed out by Davis,[2] Knunyants and Dyatkin,[3] and Gambaryan, *et al.*[6]) as a 1,5-hydrogen shift, accompanied by a double-bond shift, with the over-all electron redistribution as indicated in structure 2.



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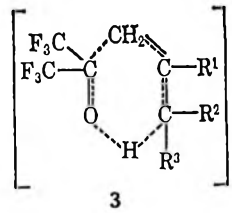
The realization that a double-bond shift occurred led to the suggestion[3,12] that the reaction mechanism is concerted and involved a six-membered cyclic transition state **3**.[13]



3

This mechanism is particularly appealing, as other noncatalyzed 1,5-hydrogen shifts involving olefins, for example, with maleic anhydride[14a] or keto esters,[14b] are believed to proceed by such a mechanism. Arguments for the concerted mechanism have been primarily based on the high stereospecificity and lack of rearrangement in the reaction products.[14,15]

In our work, the simple adducts from β-pinene and HFA or DCTFA were also formed, without appreciable (less than 1%) rearrangement. This would, at first glance, also support the view of the concerted mechanism.

Other data, however, led us to conclude that adduct formation proceeds through a dipolar, four-membered, cyclic intermediate **4** (Figure 1),[16] followed by proton migration.

These data are as follows.

(A) Reaction of HFA with an allylic compound containing another reactive functional group (epoxide) did not give the simple adduct, but a polymeric poly-

(7) For review of evidence for electrophilic character of halogens or sulfenyl halide in additions to olefins, see P. B. D. de La Mare and R. Bolton, "Electrophilic Addition to Unsaturated Systems," Elsevier Publishing Co., New York, N. Y., 1966, pp 75 and 115.

(8) See ref 7: (a) p 168; (b) p 92; (c) p 244; (d) p 32.

(9) W. Honsberg, Elastomers Department, E. I. Du Pont de Nemours and Co., personal communication, 1965.

(10) E. G. Howard, P. B. Sargeant, and C. G. Krespan, *J. Amer Chem. Soc.*, **89**, 1422–1430 (1967).

(11) P. B. Sargeant, Central Research Department, Du Pont, personal communication, 1964.

(12) (a) N. P. Gambaryan, Em. Rokhlin, Yu. V. Zeifman, C. Ching-Yun, and I. L. Knunyants, *Angew. Chem. Intern. Ed. Engl.*, **5**, 947 (1966). (b) C. G. Krespan and W. J. Middleton in "Fluorine Chemistry Reviews," P. Tarrant, Ed., Marcel Dekker, Inc., New York, N. Y., 1967.

(13) Davis postulated a six-membered cyclic intermediate, but no details were given.[2]

(14) (a) R. K. Hill and M. Rabinovitz, *J. Amer. Chem. Soc.*, **86**, 965 (1964), and earlier references quoted therein. (b) R. T. Arnold and P. Veeravagu, *ibid.*, **82**, 5411 (1960), and references therein.

(15) W. J. Middleton, *J. Org. Chem.*, **30**, 1395 (1965).

(16) A four-centered, cyclic, dipolar intermediate has been suggested in other addition reactions.[8,12b]

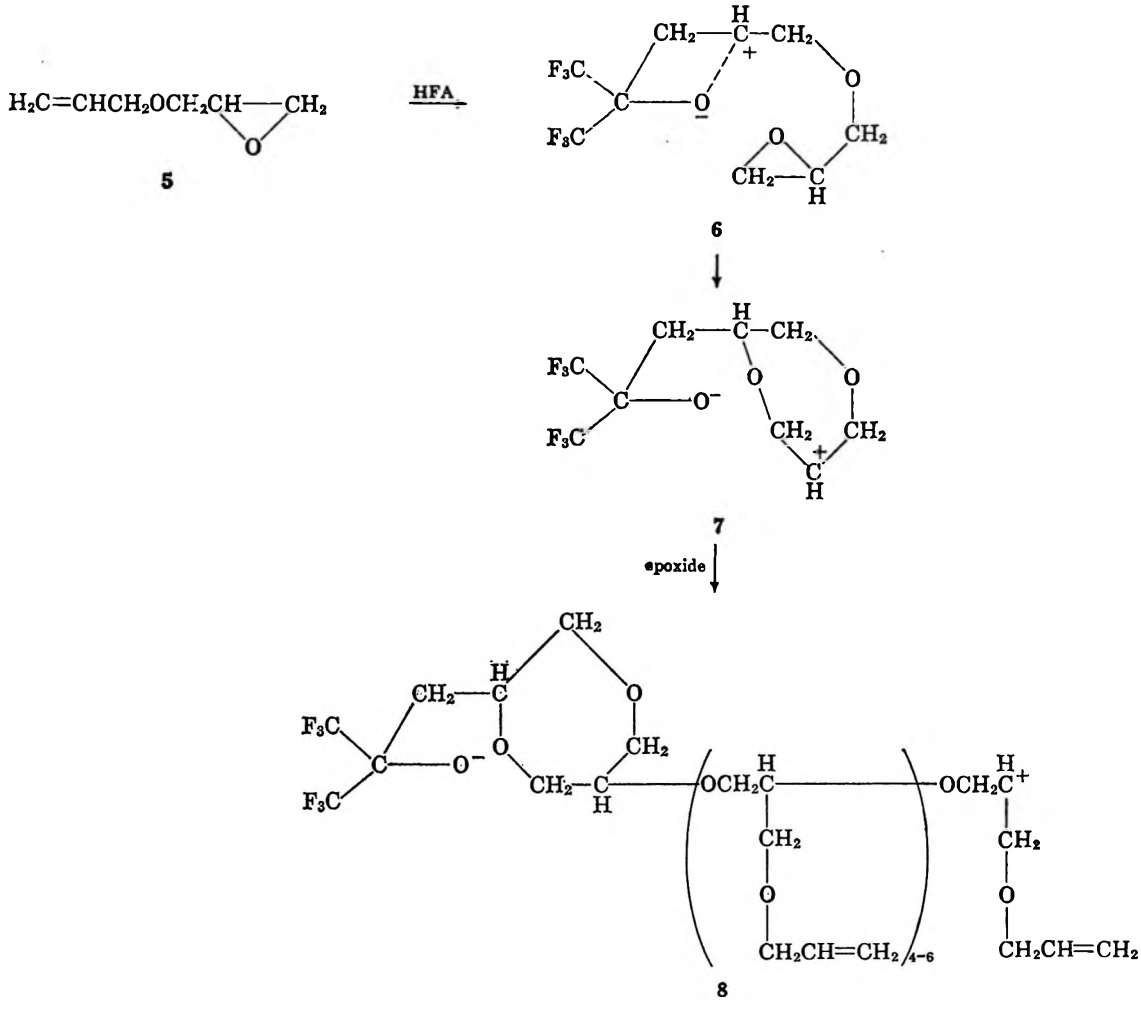


Figure 2.—Reaction of allyl glycidyl ether with hexafluoroacetone, suggested route.

ether. This polymer did not rise from direct reaction of epoxide with the HFA nor by reaction of epoxide with the usual bis(trifluoromethyl)carbinol adduct. Therefore the polymer probably resulted by trapping of an intermediate.

(B) From the trapping reaction conditions and the character of the polymeric product, the intermediate should have appreciable ionic character.

(C) Support for the ionic character of the intermediate is also given by (1) the electrophilicity of the HFA in the reaction, (2) the strong dependence of rate on electron-donating capacity of the substituents, (3) the high reaction rate with some olefins, compared with "concerted" 1,5-hydrogen-shift reactions, and (4) an appreciable solvent effect.

(D) Evidence that the intermediate is cyclic is seen (1) in the reaction characteristics (C1–C3) above, which are also characteristic of certain 1,2-cycloaddition reactions of olefins and which apparently pass through a four-membered cyclic intermediate, (2) by granting the ionic character of the intermediate, the absence of a Wagner–Meerwein type of rearrangement in formation of the HFA–β-pinene adduct, and (3) by assuming an equilibrium between the reactants and the intermediate, the lack of rearrangement of unreacted *cis*-butene-2[9] or 3,3-dimethylbutene-1.

A detailed discussion follows.

A. Interception of a Reaction Intermediate.—HFA reacted readily with allyl glycidyl ether (AGE) (**5**, Figure 2) in the presence of a trace of antioxidant, under mild conditions, in the dark, to give low polymers. With a 2:1 AGE/HFA mole ratio, heating at 75–100° for 3 hr, and an autogenous pressure of 40 psi, 95% of the AGE and about 28% of the HFA were converted into a viscous liquid product, mol wt 1085, which contained six to eight AGE units and one HFA unit. Ir and nmr spectral data indicated almost complete loss of carbonyl and epoxy groups, low terminal double-bond content, formation of some associated hydroxyl and internal double bonds, and that the high aliphatic ether content was maintained (see Experimental Section, part K).

With a lower initial AGE/HFA ratio (1:1), polymer in lower conversion was again formed, mol wt 919, which had an AGE/HFA ratio of 3:2 (see Experimental Section, part K).

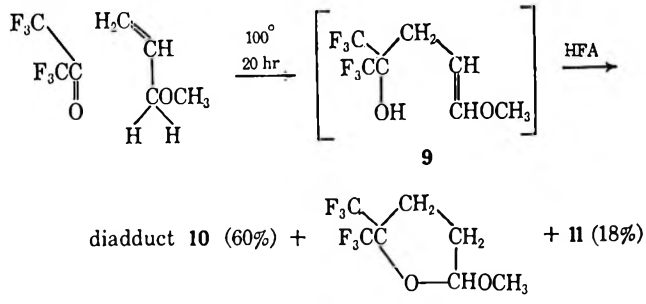
The polymers would not have resulted by direct reaction of the fluoro ketone on the epoxide group, for HFA does not react with phenyl glycidyl ether ($C_6H_5OCH_2$-$\overline{CH_2—CH_2—O}$) under these reaction conditions.

Also, the polyethers would not have resulted from an initial 1,5-hydrogen-shift reaction, followed by a secondary reaction of the *gem*-perfluorodimethylcarbinol group with the epoxide group (an SN1 substitution of the epoxide by a neutral species[17]), for reaction of such

(17) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, 1953, pp 343, 344.

an alcohol (the isobutylene–HFA adduct) with allyl glycidyl ether does not take place under these conditions. Also, in the reaction of HFA with octene-1 in the presence of phenyl glycidyl ether, the adduct of HFA and octene-1 was formed by a 1,5-hydrogen shift as usual, but no product involving the phenyl glycidyl ether was found (see Experimental Section, part N). This experiment also shows that the first epoxy ring opening in the HFA–AGE reaction was intramolecular.

These results are quite different from that obtained by reaction of HFA with allyl methyl ether. Thus Gambaryan, *et al.*,[6] under roughly equivalent conditions obtained, at a somewhat lower rate, the products **10** and **11**, expected from the usual adduct **9** resulting from a 1,5-hydrogen shift.



B. Ionic Character of the Intermediate from the Trapping Reaction.—In the HFA–AGE reaction, it appears that a cationically initiated polymerization took place. Thus, with anionic initiation the 1:1 copolymer with HFA would have formed.[18a] Also, the low nucleophilicity of the *gem*-perfluorodimethyl carbinol anion has been demonstrated.[18a]

Free-radical polymerizations of epoxides to form low polymers are known, but are difficult to initiate.[18b,19] Thus, with di-*t*-butyl peroxide initiator, phenyl glycidyl ether at 145–155° for 4 hr formed a low molecular weight polymer in 8% conversion, with 92% recovered ether.[18b] Also, if free-radical propagation was involved, some HFA would be expected to be incorporated along the polymer chain.[10] Further, hydroquinone inhibitor was present.

Under these conditions a biradical intermediate appears too unreactive[20] to initiate epoxy polymerizations.

The suggested reaction course is shown in Figure 2. After initiation to form the cyclic dipolar intermediate **6**, reaction proceeds by intramolecular attack of the carbonium ionic center on the epoxy oxygen. (Perhaps the six-membered cyclic transition state for this step encourages this reaction course rather than the 1,5-hydrogen shift.) Epoxy ring opening then may lead to the more stable (secondary) carbonium ion **7**. This mode of attack predominates in acid-catalyzed ring openings of substituted epoxides.[21,17] The latter carbonium ion then reacts with other epoxide groups available in the solution. The increased incorporation of HFA in the second example may have resulted from secondary reaction of excess HFA with the pendant allyl groups in the polymer **8** (Figure 2). However, further work is necessary to determine the polymer structure in detail.

In the propagation, step, it appears that a conventional cationic step is involved. This is suggested by the reaction of HFA with a mixture of AGE and phenyl glycidyl ether. In this case, some phenyl glycidyl ether was incorporated in the polymer. When the AGE, phenyl glycidyl ether, and HFA were present in the reactant mixture in a 1:1:1 mole ratio, the resulting ratio in the polymer was 4:1:2.4 (see Experimental Section, part L). This further supports the view that the reaction is stepwise, and that the initial intermediate has ionic character, and against the view that the epoxy group in AGE participates in the HFA–allyl group reaction in a concerted fashion.

The difference in activity of the epoxy groups in AGE and in phenyl glycidyl ether may also involve the former being within the "solvation sphere," and perhaps more advantageously oriented for reaction with the dipolar cyclic intermediate.

These results, then, may be considered as supporting evidence that "intimate" ion pairs[22] resulting from *cis* additions can exist as intermediates[8c] with the attached epoxy group intercepting the initimate ion pair before the latter reaches the solvent-separated, ion-pair stage.

In any case, the utility of this type of trapping agent for detecting an intermediate as well as demonstrating its ionic character is shown.

C. Substituent Effects and Ionic Character of the Intermediate.—It was previously mentioned that the effects of substituents on the rate of formation of the HFA adducts show typical electrophilic behavior for the HFA. This usually suggests a carbonium ion mechanism.[7] However, such substituent effects are also qualitatively similar to those in 1,2 cycloadditions of 1,1,2,2-dichlorodifluoroethylene to olefins,[20,23] which are believed to proceed *via* a two-step mechanism through a cyclic "biradical" intermediate[23] (thus resembling at least geometrically the four-membered dipolar ion intermediate postulated for the HFA–olefin reactions).

A biradical intermediate does not appear to be involved in the HFA–olefin reactions, based on (a) the interception of the intermediate with an epoxy group (as mentioned above), (b) the slower reaction of HFA with 2-chloropropene than with propylene (the reverse would be expected for a biradical intermediate, for the chlorine atom, by electron delocalization, should stabilize the biradical[20]), and (c) the lack of ring-opened products (which have been observed in peroxide-catalyzed reactions of β-pinene with chloroalkanes[24,25]).

The great differences in rate of adduct formation for olefins with electron-donating *vs.* electron-withdrawing substituents (see Chart I) are characteristic of reactions involving carbonium ion intermediates.[7]

The high reaction rate for many of the olefins with HFA has not been observed for previously described

(18) (a) N. L. Madison, Polymer Preprints, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, p 1099; (b) A. Otu, M. Okano, and R. Oda, *Bull. Chem. Soc. Jap.*, **37**, 570 (1964).

(19) A. E. Gurgiolo, "Reviews in Macromolecular Chemistry," Vol. I, 1966, pp 39–193; see p 124.

(20) P. Bartlett and L. K. Montgomery, *J. Amer. Chem. Soc.*, **86**, 628 (1964), and references quoted therein.

(21) H. C. Chitwood and B. T. Freure, *ibid.*, **68**, 680 (1946).

(22) S. Winstein and G. C. Robinson, *ibid.*, **80**, 169 (1958).

(23) P. D. Bartlett, G. Wallbillick, and L. K. Montgomery, *J. Org. Chem.*, **32**, 1290 (1967), and earlier references.

(24) D. M. Olroyd, G. S. Fisher, and L. A. Goldblatt, *J. Am. Chem. Soc.*, **72**, 2407 (1950).

(25) G. Du Pont, R. Dulon, and G. Clement, *Bull. Soc. Chim. Fr.*, 257 (1951).

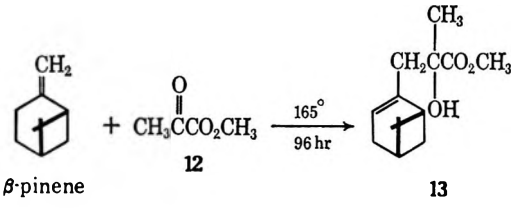
TABLE II

EFFECTS OF SOLVENTS ON REACTION RATES

Solvent	Dielectric constant (20°)	TCNE[a] + p-MS, k_2 (10^4)	BTFMDCNE + TBVS,[b] % convn	Diels–Alder reactions,[c] % convn	DCTFA[d] + DIB	
					% convn[e]	k_2 (10^8)[f]
CH_2Cl_2	9.08	1600	55.0		18	290 + 40
EtOAc	6.40	330	83.0		10	160
Et_2O	4.34	2.8			2	30
CCl_4	2.24		2.3			
Cyclohexane	2.07	0.04			~0.5	~8
CH_2Cl_2/C_6H_2		40,000		<7	~30	
CH_2Cl_2/Et_2O		570			6	
CH_2Cl_2/CCl_4			24			

[a] Tetracyanoethylene with p-methoxystyrene. Data of Wiley,[33] 0.10 *M* in p-MS, 0.006 *M* in TCNE, 25°. [b] *cis*-1,2-Bis(trifluoromethyl)-1,2-dicyanoethylene with *t*-butyl vinyl sulfide (data of Proskow, *et al.*[34]). Reactant concentration was 10% (w/v) of solution, 25°. Reaction rate estimated by disappearance of the charge-transfer complex. [c] See ref 33. [d] *sym*-Dichlorotetrafluoroacetone with 2,4,4-trimethylpentene-1: 0.6 *M* DCTFA, 1.0 *M* DIB, 25 ± 2° (see also Experimental Section, part F). [e] Conversion into adduct at 20 hr. [f] Calculated as second-order rate constant.

uncatalyzed 1,5-hydrogen-shift reactions believed to proceed in concerted fashion.[14b,26-29]



As examples, the reaction of β-pinene with a ketone containing a reactive carbonyl group (methyl pyruvate **12**) to form the 3,4-unsaturated alcohol **13** was reported to require 96 hr at 165° to reach equilibrium (55% conversion).[14b] Also, the reaction of β-pinene with acrylonitrile took 4 hr at 235° to attain 42% conversion into the adduct.[26] On the other hand, the β-pinene–HFA reaction proceeded in high conversions in a few minutes at 25°. (The reaction of acetylene dicarboxylic ester with isopropylideneamine to give a diene amine by a 1,5-hydrogen shift proceeded under mild conditions, and a 1,4 dipolar intermediate was postulated. No direct evidence for the mechanism was presented.)[30]

Apparently, the HFA–olefin reactions proceed as readily as the analogous Diels–Alder reactions (HFA with isobutylene *vs.* HFA with isoprene[31]). This is unusual in other systems when relative rates of 1,5-hydrogen shifts *vs.* Diels–Alder cyclization are compared.[28,29]

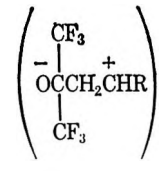
The carbonyl group of HFA is electron deficient because of the electron-withdrawing effect of the trifluoromethyl groups, and so would resemble a weakly polarized olefinic group. This is supported by the low nucleophilic activity of HFA.[10,12] Thus, 1,5-hydrogen shifts in HFA–allylic olefin reactions would be expected to occur with similar difficulty to the above-described "concerted" rearrangements.

The reaction of DCTFA with 2,4,4-trimethylpentene-1 (diisobutylene) proceeded slowly enough to readily follow the reaction at room temperature. It was observed, qualitatively, that an appreciable solvent effect existed, probably larger than that expected for concerted reactions.

Thus, Diels–Alder reactions are reported to show very small solvent effects, with rates slower in the more polar solvents (acetone, acetic acid) than in chloroform or carbon tetrachloride and with maximum differences in reaction rate in these solvents being *ca.* sevenfold.[32,33]

On the other hand, the reaction of DCTFA with diisobutylene (DIB) in various solvents led to the results shown in Table II (see Experimental Section, part F). The solvent effects on the rate through this representative group differed by about 30-fold, and rates increased with increased polarity of the medium. The relative effects of methylene chloride, ethyl acetate, and diethyl ether on reaction rate were considerably smaller than those observed in the 1,2-cycloaddition reactions of p-methoxystyrene (p-MS) with tetracyanoethylene, by a factor of about 100. On the other hand, the relative effects of these solvents on the DCTFA–DIB reaction were about the same as those found in the 1,2-cycloaddition reaction of *cis*-1,2-bis(trifluoromethyl)-1,2-dicyanoethylene with *t*-butylvinyl sulfide.[34] In the latter, strong evidence existed for a four-membered cyclic zwitterion intermediate.[34]

D. Evidence for a Cyclic Intermediate.—If an intermediate with considerable ionic character of the



type described above existed in extended form, skeletal rearrangements would be expected for molecules capable of Wagner–Meerwein rearrangements, such as β-pinene, camphene, or neohexene-1.

In the reaction of DCTFA with β-pinene, high conversions and essentially quantitative yields of a monoadduct were obtained under mild conditions.

The nmr and ir spectra of the high boiling fraction indicated only one product, the 3,4 internally double-bonded adduct having only one vinylic hydrogen (see Experimental Section, parts G and H). That

(26) C. J. Albisetti, N. G. Fisher, M. J. Hogsed, and R. M. Joyce, *J. Amer. Chem. Soc.*, **78**, 2637 (1956).

(27) A. G. Smith and B. L. Yates, *J. Org. Chem.*, **30**, 2067 (1965).

(28) J. Wolensky, B. Chollar, and M. D. Baird, *J. Amer. Chem. Soc.*, **84**, 2775 (1962).

(29) J. Ross, A. I. Gebhart, and J. F. Gerecht, *ibid.*, **68**, 1373 (1946).

(30) R. Huisgen and K. Herbig, *Ann. Chem.*, **688**, 98 (1965); see also R. Huisgen, M. Morikawa, D. Breslow, and R. Grashey, *Chem. Ber.*, **100**, 1602 (1967).

(31) W. Linn, *J. Org. Chem.*, **29**, 3111 (1964).

(32) L. J. Andrews and R. M. Keefer, *J. Amer. Chem. Soc.*, **77**, 6287 (1955).

(33) D. W. Wiley, to be published.

(34) S. Proskow, H. E. Simmons, and T. L. Cairns, *ibid.*, **88**, 5254 (1966).

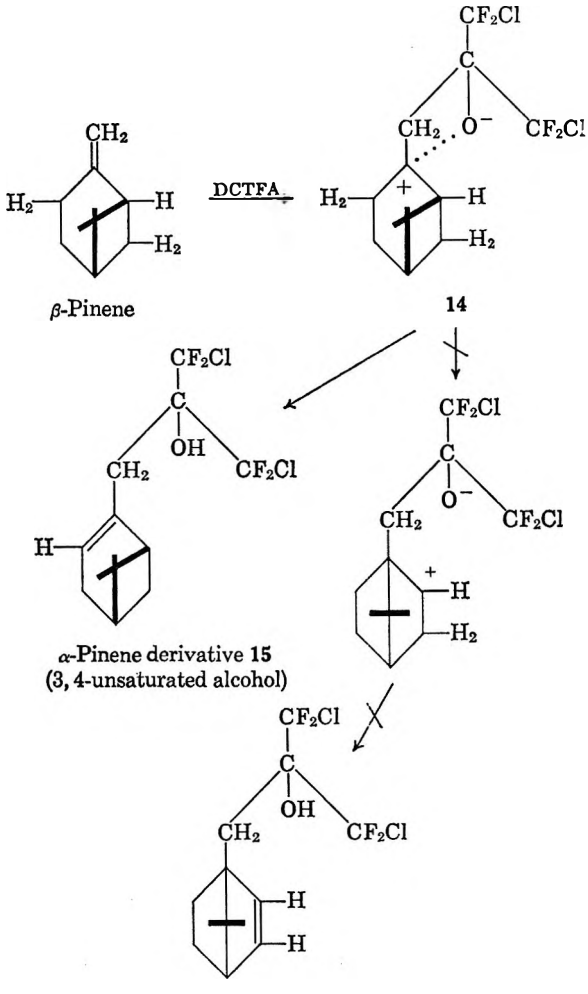


Figure 3.—Reaction of β-pinene with DCTFA.

is, the adduct was the one expected from β-pinene by a 1,5-hydrogen shift *without* skeletal rearrangement **15** (Figure 3).

The same result was obtained on examining the undistilled reaction product. Therefore this adduct did not arise by secondary thermal reactions. Also equivalent results were obtained in reaction of β-pinene with HFA (see Table I and the Experimental Section, part G). The vpc and nmr spectral data indicate that less than 1% of the rearranged product is present.

We presume that β-pinene–HFA reaction proceeds by the same mechanism as that for the AGE–HFA reaction. This assumption is supported by the high reactivity of β-pinene toward adduct formation. The product expected if skeletal rearrangement had occurred, **16**, would be the one expected if reaction occurred either by "nonclassical" carbonium ion mechanism or by rapidly equilibrating "classical" ions.[35] The lack of skeletal rearrangement indicates neither of these.

β-Pinene has been used frequently as a probe for carbonium ion intermediates[14b,15,16] for Wagner–Meerwein-type rearrangements or ring-opening reactions occur overwhelmingly with this reactant under solvolytic conditions or with most acid catalysts which ordinarily lead to carbonium ions.[36]

Although it is recognized that occurrence or nonoccurrence of skeletal rearrangement in reaction of bicyclic compounds is *per se* not a criterion for the presence or absence of mesomeric or classical cation intermediates,[37] usually the extent of rearrangement can be accounted for by considering the degree of kinetic control of the reaction rate. In the β-pinene systems, however, the reported rearranged products are those expected with either thermodynamic or kinetic control. As a result, lack of skeletal rearrangement in β-pinene reactions has been taken as practically conclusive evidence for a concerted mechanism.

On the other hand, hydrogen chloride may be added to the double bond of either α- or β-pinene in nonpolar or weakly polar nonsolvolyzing solvents (hydrocarbons, diethyl ether) at reduced temperatures (−70 to −15°), to give the same "pinene hydrochloride," with very little skeletal rearrangement.[38] This reaction has long been considered to involve carbonium ions as intermediates.[8]

Brown and Liu, in additions of HCl or DCl to α-fenchene, apobornylene, or camphene also observed a very low level of rearrangement (≤10%), in ethyl

(35) H. C. Brown, K. J. Morgan, and F. J. Chloupek, *J. Amer. Chem. Soc.*, **87**, 2137 (1965).

(36) J. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 186.

(37) See ref 36, pp 136–137.

(38) J. L. Simonsen, "The Terpenes," Vol. II, Cambridge University Press, London, 1940, pp 172, 202.

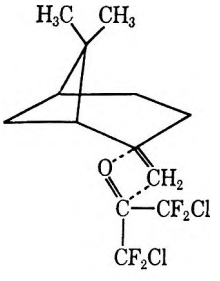
ether or methylene chloride solvents at 0 to −78°.[39] Additions were also shown to be *cis*.[39]

Other olefin addition reactions in which rearrangements do not occur are hydroborations,[40,41] oxymercurations,[42,43] sulfenyl halide additions,[44] and acid-catalyzed hydrations.[45,7d] In all of these cases intermediates obtained by *cis* additions have been suggested.[8]

The addition of chlorine in common solvents to strained bicyclic olefins also appears to proceed by a *cis* addition.[46] De La Mare and Bolton suggest that such reactions proceed through a transition state or intermediate with considerable carbonium ionic character, with a structure similar to that suggested above the HFA–olefin reactions. They also suggest that such a transition state or intermediate lies earlier on the reaction path than the carbonium ion intermediate, and that each intermediate may react directly to form a product.[8b,c]

The lack of rearrangement with such intermediates may be related to geometrical limitations to orbital interpretration. In the case of HFA–olefins, the carbonyl group and the double bond of the olefin approach in parallel planes, orthogonal to the direction of the covalent bond to be formed, to get π-orbital overlap, and the substituents on the olefin remain essentially coplanar through the transition state and in the intermediate **4** (Figure 1). This is shown in **17** for DCTFA with β-pinene. Drieding models indicate (for either *exo* or *endo* addition) that the resulting orientation for the potentially migrating C—C bond is certainly not coplanar, let alone coaxial, with the C^{+}-----O^{-}-directed bond in the intermediate.

Therefore orbital penetration is very low, and the rate of skeletal rearrangement in the β-pinene moiety is small compared with the 1,5-hydrogen shift.



17

Winstein and coworkers[47,48] have shown that even in the presence of ionizing solvents and bases at least as strong as H_2O (solvolyzing systems), if the geometry is unfavorable for bond delocalization in the carbonium ion, then rearrangement occurs after the rate-determining ionization step. Note that the β-pinene–HFA reaction was carried out neat, in a low polarity medium,[49] in which intimate ion pairs would be encouraged and with relatively high-directed bond character.[22]

Discussion

A.—If the above-described mechanism has validity, noncatalyzed reactions of HFA with *non*allylic olefins could proceed through the same intermediate. This view appears to have support in the reaction of HFA with styrene, in which low molecular weight polystyrene is rather slowly formed and most of the polymer contains no HFA end group (Experimental Section, part N).

Thus the cyclic dipolar intermediate may be formed first, followed by polymerization *via* cationic initiation. Support for the cationic mechanism is (1) propagation in the presence of hydroquinone (not biradical)[50a] and (2) the rather sluggish rate coupled with low molecular weight (high chain transfer to monomer).[50a]

Another example is the reaction of HFA and DCTFA with dienes in the Diels–Alder reaction. These occurred extremely readily below 0°.[31] Therefore they may be considered two-step reactions in which the first step involves the formation of the four-centered dipolar ion (the ion stabilized by allylic resonance), followed by ring closure through ion-pair collapse.

A similar situation probably exists for the vinyl ethers, with the formation of oxetanes.[12b,50b]

B.—The cylic intermediates to the adducts formed from HFA and allylic olefins (like those of 1,2-bis(trifluoromethyl)-1,2-dicyanoethylene and electron-rich alkenes[34]), would be formed in accordance with the Hoffmann–Woodward selection rules, which predict that noncatalyzed concerted four-membered cycloadditions (no intermediate) are disfavored thermal processes, and, on the other hand, discrete four-membered cyclic intermediates are permitted.[51]

Previous workers showed that addition of electrophilic polar reagents to strained bicyclic systems (HCl, oxymercuration) proceed in an *exo* fashion, even with *gem*-dimethyl groups in the 7 position of bornene systems.[39,43] In the addition of HFA to β-pinene, molecular models (Drieding) show no appreciable steric problems with either an *exo* or an *endo* approach. With an *exo* addition in this case, support is offered for the view that a nonclassical ion is not necessary to explain the *exo* addition in these systems.[39]

General Conclusions

A.—A four-centered cyclic dipolar intermediate is present in addition reactions of HFA or DCTFA with nonhindered olefins, including strained bicyclic olefins, and this intermediate can directly participate in reactions with nucleophilic groups.

B.—Attempts are often made to determine the existence of a reaction intermediate by "trapping" the intermediate. Results may be negative, however, if the potentially reactive group is present only in the solvation sphere. Positive results may be obtained by using appropriate polyfunctional reagents. Allyl glycidyl ether appears to be particularly useful in noncatalyzed reactions, and also indicates the polarity of the intermediate.

(39) H. C. Brown and K. T. Liu, *J. Amer. Chem. Soc.*, **89**, 3900 (1967), and also earlier references.

(40) G. Zweifel and H. C. Brown, *ibid.*, **86**, 393 (1964).

(41) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962.

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

(43) H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **89**, 1525 (1967).

(44) See ref 36, pp 161–162.

(45) P. Riesz, R. W. Taft, Jr., and R. H. Boyd, *ibid.*, **82**, 4729 (1960).

(46) S. J. Cristol, F. R. Stermitz, and P. S. Ramsey, *ibid.*, **78**, 4939 (1956).

(47) S. Winstein and D. Trifan, *ibid.*, **74**, 1151 (1952).

(48) S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan, and H. Marshall, *ibid.*, **74**, 1127 (1952).

(49) Carl Brock of the Orchem Department, Du Pont, has found the apparent dielectric constant of 20% HFA–H_2O in toluene to be 2.47 at 25°.

(50) (a) C. Walling, *ibid.*, **66**, 1602 (1944); (b) H. R. Davis, U. S. Patent 3,164,610 (1965).

(51) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2045 (1965).

C.—A reaction is often considered concerted by a demonstration of lack of skeletal rearrangement in the reaction products. This has been considered particularly strong evidence if the alternative mechanism involves a "carbonium ion" intermediate for which rearrangement is the rule.

This work indicates, however, that in reactions which appear to involve *cis* additions no skeletal rearrangement need be expected. This also implies that an intermediate is formed which is cyclic and had existed for a negligible period in the open-chain form.[20,34]

D.—As the above conclusions pertain specifically to 1,5-hydrogen shift (thermal addition) reactions of olefins with asymmetric dienophiles (such as formaldehyde, sulfur trioxide, chloral), these reactions, previously considered concerted,[14b] should be reexamined, using appropriate polyfunctional trapping reagents.

Experimental Section[52]

A. Preparation of the Adduct of HFA with Propylene [CH_2=$CHCH_2C(CF_3)_2OH$].—Hydroquinone (0.1 g) was placed in a dry 300-cc stainless steel shaker tube, which was flushed with nitrogen and cooled to −70°, and HFA (83 g, 0.5 mol, Orchem Department, E. I. du Pont de Nemours and Co., used without further purification) and propylene were introduced (21 g, 0.5 mol). The tube was then sealed, shaking was started, and the temperature was brought up in stages. Thus, at 50°, the autogeneous pressure was 250 psi, with no pressure drop or exotherm observed over a 1-hr period. The temperature was then raised to 75°, and pressure reached 310 psi; at 130° it was 375 psi, and at 125° it was 400 psi. At 150° a slow pressure drop was observed (440 → 435 psi), and so the tube was shaken at this temperature for 2.5 hr. The tube was then cooled and vented, and 18 g (17% conversion) of the adduct was obtained (see Table I).

B. Preparation of the Adduct of HFA with 2-Chloropropene-1 [CH_2=$C(Cl)CH_2C(CF_3)_2OH$].—2-Chloropropene-1 (38 g, 0.5 mol, Columbia Organic Chemicals Co., used directly), hydroquinone (0.1 g), and HFA (83 g, 0.5 mol) were allowed to react as in part A (see also Table I). No pressure drop was observed until the internal temperature reached 164°, whereupon it was held at this temperature for 4 hr. The rather steady rate of pressure drop at 164° of about 20 psi/hr indicates that the reaction is not appreciably reversible at these temperatures.

About 60 g of liquid products were obtained which on a single distillation through a 24-in. platinum gauze spinning-band column gave *ca.* 12.0 g (10%) composed principally of the adduct; infrared absorption (CCl_4) included bands at 2.9 (sharp, —OH) and at 6.1 μ (—C=CH_2); nmr peaks were at δ 5.48 (1.9 H, multiplet, >C=CH_2), 3.86 (1 H, broad, O—H), and 2.98 (1.9 H, singlet, —CH_2—).

Anal. Calcd for $C_6H_5ClF_6O$: C, 29.70; H, 2.07; Cl, 14.64; F, 47.00. Found: C, 30.41; H, 2.57; Cl, 14.06; F, 45.51.

C. Preparation of the Adduct of HFA with Allyl Chloride [$CHCl$=$CHCH_2C(CF_3)_2OH$].—Allyl chloride (38 g, 0.5 mol, Eastman White Label), HFA (83 g, 0.5 mol), and hydroquinone (0.01 g) reacted as in part A with no pressure drop observed even at 165° for 4 hr (600 psi developed). The tube was then cooled, and 40 g of nonviscous liquid was obtained. Distillation gave 3 g (3%) of the adduct; infrared absorption (CCl_4) showed bands at 2.8 (OH), 8.1, 8.6, 9.3, 13.9 (C—F), and 6.0 μ (C=C).

Anal. Calcd for $C_6H_5ClF_6O$: C, 29.70; H, 2.07; Cl, 14.64. Found: C, 29.72; H, 2.18; Cl, 14.35.

D. Preparation of the Adduct of 2,4,4-Trimethylpentene-1 (Diisobutylene) and Dichlorotetrafluoroacetone (DCTFA) [$(CH_3)_3CCH_2C$(=CH_2)$CH_2C(CF_2Cl)_2OH$].—DCTFA (28 g, 0.14 mol, Allied Chemical Co.), cooled in ice, was mixed with 11 g (0.10 mol) of diisobutylene (Phillips Chemical Co., pure grade).

The solution was then heated to reflux in a flask fitted with a magnetic stirrer, reflux condenser, and thermometer. The internal temperature rose from 57 to 70° over a 5-hr period. On one distillation, 16 g (50%) of essentially the adduct was obtained (see Table I); the infrared absorption (CCl_4) included a peak at 2.9 μ (OH); the nmr peaks (neat) were at δ 5.15 (2 H, singlet, =C=CH_2), 3.65 (1 H, singlet, —OH), 2.80 (2.0 H, singlet, —CH_2—$C(CF_3)_2$—), 2.05 (2.3 H, singlet, —CH_2—), and 0.90 (9.1 H, singlet, —$C(CH_3)_3$); the nmr peaks (CCl_4) of diisobutylene starting material were at δ 4.80, 4.60 (2 H, two broad singlets, =C=CH_2), 1.90 (2 H, singlet, —CH_2), 1.76 (3 H, multiplet, —CH_3), and 0.90 (9 H, singlet, —$C(CH_3)_3$).

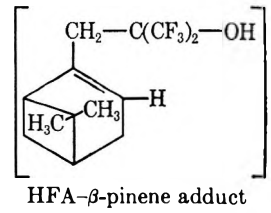
The nmr spectra of the product corresponded with the externally double-bonded structure. The peak intensity ratio for the external double-bond structure was calculated to be 1:2:2:2:9, and that for the internal double-bond structure was calculated to be 1:1:2:3:9. (The ratio actually found was 1:2:2:2.3:9.1.)

Anal. Calcd for $C_{11}H_{16}Cl_2F_4O$: Cl, 23.66. Found: Cl, 23.08.

E. Reaction of Diisobutylene (DIB) and DCTFA at Room Temperature. Search for Biproducts, Intermediates by Nmr.—Reaction was carried out by dissolving 0.2 g of the olefin in 0.3 g of DCTFA at −70° in an nmr tube and quickly bringing the tube in the spectrometer to room temperature. The nmr data for the DIB and the adduct were identical with the higher temperature case. If the cyclic ether adduct is formed to any extent, the peak due to —C—$(CH_3)_3$ compared to that due to H_2C=C< should increase from the initial 9:2 ratio. Also the ratio of peaks due to —CH_2—$C(CF_2Cl)_2$/H_2C=C< should become >1. The initial ratio of the 0.9- to 4.7-ppm band was 4.8 (theory 4.5). The 2.9- to 5.2-ppm band ratio was 1.08 (theory 1.0). These ratios remained essentially constant over a period of 48 hr at room temperature, with conversion into the adduct rising to 55%. Also, there was no evidence of complex formation between the DIB and the DCTFA by band splitting, chemical shift, or solution color.

F. Reaction of DIB with DCTFA. Effect of Solvent on Reaction Rate.—Qualitative comparisons were obtained by observing the intensity of the infrared absorption band associated with the —$C(CF_2Cl)_2$—OH group in the adduct (2.82 μ in cyclohexane and methylene chloride, 2.90 μ in ethyl acetate, 3.05 μ in diethyl ether). The band intensity was related to adduct concentration by comparison with solutions of known concentration. The reactions were carried out in the following way. DCTFA (1.19 g) was added to 1.12 g of DIB in the solvent tested so as to give 10.0 ml of solution (0.6 *M* DCTFA, 1.0 *M* DIB). Mixing was carried out below −70° in the presence of 0.001 g of hydroquinone. The solvents were reagent grade, dried with Linde Molecular Sieve 5A, and duplicate runs were made. After mixing, samples were withdrawn with a syringe and compared in the same infrared cell. Initial data were taken 5 min after the mixing operation. Conversion differences between duplicates were less than 10%.

G. Preparation of the Adduct of HFA and β-Pinene.—β-Pinene [bp 65–66° (23 mm), 13.8 g, 0.1 mol, containing 10% α-pinene by nmr[53]], hydroquinone (0.1 g), and HFA (17 g, 0.1 mol) reacted as in A. The tube was brought up to room temperature with shaking for 2 hr. *Ca.* 25 g of colorless, nonviscous liquid was obtained. On standing, large crystals (~3 g) slowly formed. About 18 g of the liquid phase was distilled to give 9 g of the adduct which crystallized on standing, mp 33–34°, the same value as that of the crystals which originally separated (see Table I). Infrared absorptions (CCl_4) were found at 2.9 (sharp, —OH), 7.8–9.0, 9.8, 13.9, 14.8 (C—F), 6.1 (vw, C=C), and 12.3 μ (w, HR_1C=CR_3R_2).[54] No peak was found near 14.3 μ, characteristic



HFA–β-pinene adduct

(52) Boiling points are uncorrected. The proton nuclear magnetic resonance spectra were obtained on a Varian Associates A-60 nmr spectrometer, and chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Spectra were determined on 10% solutions in carbon tetrachloride unless otherwise indicated. Infrared spectra were obtained on a Perkin-Elmer Infracord and calibrated with polystyrene. The 3,3-dimethylbutene-1 was obtained from Sinclair Chemical Co. and the methacrylonitrile was obtained from the Vistron Corp.

(53) "High Resolution NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, entries no. 274 and 272.

(54) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, pp 51, 52.

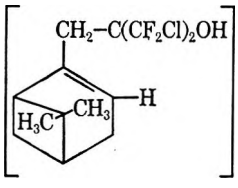
of C—H stretching in *cis* —CH=CH— structures of the norbornene type.[54] The nmr peaks (CCl_4) at δ 2.97 (1 H, broad, —OH), 5.60 (1 H, broad, —CH=C—), 2.64 [2 H, singlet, —CH_2—$C(CF_3)_2$—], 1.30, (3.1 H, sharp singlet, —CH_3), and 0.84 (3 H, sharp singlet, —CH_3) indicate only a single product, the simple adduct without rearrangement.

Thus the peak at δ of 2.97 ppm was proved due to the —OH group, as it disappeared on shaking with D_2O. The peak at δ 5.60 ppm had an area equivalent to one vinylic proton, and is the only peak downfield of the 2.97-ppm peak. The magnitude and shift direction is as expected for a product with an α-pinene skeleton (see also discussion on reaction of β-pinene with DCTFA). The peaks at δ 0.84 and 1.30 ppm, attributed to the *gem*-methyl groups, are essentially at the same positions as the *gem*-dimethyl groups of α-pinene, supporting further the location of the double bond in the adduct (the *gem*-dimethyl peaks in β-pinene are at δ 0.70 and 1.20 ppm and in *p*-anisyl bornylene are at δ 0.80 and 0.92).[55] Vpc indicated purity of over 98% based on relative area of the peaks and total volume of collected products. This indicates that negligible reaction or dissociation of the adduct occurs on the vpc column.[56]

With this information about the product stability in hand, examination of the vpc of the undistilled, unheated crude product (and correcting for the separated crystals) indicated the unrearranged adduct to be present in about 81% conversion, 99% yield, with four more volatile impurities present in about 1% total concentration.

Anal. Calcd for $C_{13}H_{16}F_6O$: C, 51.66; H, 5.30; F, 37.75. Found: C, 51.31; H, 5.32; F, 37.46.

H. Reaction of β-Pinene with DCTFA.—Mixing 14 g (0.10 mol) of β-pinene with an excess of DCTFA (35 g, 0.17 mole) at



−70° and warming slowly resulted in an exothermic reaction, and the temperature rose to 0° within a few minutes. After 1 day at room temperature the solution was distilled, giving 21 g (66%) of the adduct (see Table I).

The infrared spectrum indicated the presence of an internal double bond similar to that in α-pinene derivatives, *i.e.*, absorption (CCl_4) at 6.05 (vw, C=C) and 12.6 μ (w) (CH out-of-plane deformation of trisubstituted ethylenes).[54] Also there was no peak near 14.3 μ which is characteristic of norbornene [CH stretching of *cis* CH=CH[54]]. Other peaks were at 2.95 (OH), 8.3–9.8 (s), and 14.6 μ (w) [—$C(CF_3)_2$—OH]. The nmr analysis (CCl_4) supported this conclusion; *i.e.*, only one methynyl proton was present [δ 5.7 (1 H, broad)], with the chemical-shift magnitude and direction expected on substituting a —$C(CF_3)_2$—OH group for H (δ 5.7 for the adduct compared to δ 5.15 for α-pinene, *vs.* δ 6.0 for norbornene).[57] Other nmr peaks were at δ 3.3 (1 H, broad, —OH), 2.8 (1.8 H, multiplet, —CH_2 *exo*), 1.31 (2.8 H, singlet, —CH_3), and 0.86 (2.9 H, singlet, —CH_3). The position of the *gem*-dimethyl groups support the α-pinene structure in the product.

The column holdup and residue was identical with the distilled adduct in viscosity and infrared spectrum. No unexpected infrared peaks were observed for the forerun.

Anal. Calcd for $C_{13}H_{16}Cl_2F_4O$: F, 22.68. Found: F, 22.29.

I. Treatment of α-Pinene with DCTFA.—On mixing α-pinene with DCTFA at room temperature for 20 hr, only a slight reaction occurred. That is, traces of absorption in the infrared (CCl_4) at 5.75, 6.05, 7.95, 8.1 (shoulder), 11.45, and 11.65 μ indicate presence of small amounts of an externally double-bonded adduct, particularly in the residue after distillation.

J. The Adduct of HFA and α-methylvinyl methyl ether [$CH_3OC(=CH_2)CH_2C(CF_3)_2OH$] was obtained by using reaction conditions given in part A (see Table I). Infrared analysis (CCl_4) showed absorptions at 2.95 (mod.,[58] associated OH), 6.0 (H_2C=C=), and 7.8 (s), 8.0 (s), 8.3 (s), 8.7 (s), 9.3 (s), and 9.7 μ (s) (C—F). Bands at 10.1 μ (mod.), 10.7 (mod.) were present in the original ether but were of low intensity. New bands were also found at 13.7 μ (mod.) and 14.9 μ (mod.). Missing from the original ether were the bands that appeared at 6.2 (mod.), 9.2 (s), and 12.7 μ (s). No appreciable differences in spectra were observed whether the analysis was run neat or as a 1% solution in CCl_4 (association by internal hydrogen bonding). The nmr peaks (neat) were at δ 5.15 (1 H, broad, —OH), 4.3 (2.1 H, multiplet, >C=CH_2), 3.7 (3.2 H, singlet, CH_3—O), and 2.85 [2.1 H, singlet, —CH_2—$C(CF_3)_2$—].

Anal. Calcd for $C_7H_8F_6O_2$: C, 35.30; H, 3.36; F, 47.90. Found: C, 35.79; H, 3.54; F, 47.22.

K. The Reaction of HFA with allyl glycidyl ether (AGE) was carried out according to the procedure in part A using 23 g (0.2 mol) of AGE [Shell Chemical Co., bp 76° (53 mm)], 0.2 g of hydroquinone, and 17 g (0.1 mol) of HFA. At 75–79°, a slow pressure drop was observed (pressure fell from 40 psi to 35 psi in 1 hr). The rate of pressure drop was slightly greater at 100°; after 3 hr the pressure was 15 psi. The clear viscous product was placed in a spinning-band column under vacuum to constant weight to remove unreacted material.

The residue after removing volatiles (HFA, AGE) was a viscous liquid (27 g) with bp >150° (1 mm) and mol wt 1085 (boiling point elevation in benzene). The elemental analyses indicate a minimum HFA content of 14, 16, and 13 mol %, respectively, or 1 mol of HFA/6.1–6.7 mol of AGE (minimum mol wt 862–897).

Anal. Calcd for 1 mol of (C_3H_6O)/6.5 mol of $(C_6H_{10}O_2)$ or $C_{42}H_{65}O_{14}F_6$: C, 55.6; H, 7.15; F, 12.6. Found: C, 55.33; H, 6.98; F, 12.64.

By ebulliometry the mole ratio would be 1 mol of HFA/8 mol of AGE. The infrared spectrum (neat and in carbon tetrachloride) indicated the loss of some double bond (3.2 μ) and epoxy content (11.8 μ) from the AGE and loss of the carbonyl group of the HFA (5.4 μ). Also, hydroxyl groups, intermolecularly associated, were formed (2.9–3.1 μ). The product was not soluble in 5% aqueous sodium hydroxide. This information, coupled with the high aliphatic ether content which was maintained (9.0 μ), and increased —CH— absorption (7.2 μ), suggests the formation of dioxane and/or polyethylene glycol units associated with the hydroxyl groups.

A new absorption at 14.0 μ supports the idea of chains containing at least three aliphatic carbon atoms, expected if the HFA added to the allyl double bond (also phenyl glycidyl ether did not react with HFA under these conditions).

Stronger absorption at 5.9 μ (still weak) suggests the formation of new internal double bonds. These double bonds could arise in a termination step.

The nmr spectrum also indicated the complete loss of the epoxide group by loss of a multiplet (relative area 2) at δ 2.5 (>C—CH_2—O) and by loss of a multiplet (relative area 1) at δ 3.0 (—CH—C(O)<).

Also, the nmr analysis indicated formation of ethylene glycol ether groups and some disappearance of the terminal allylic double bond [ratios of band areas of δ 5.7 (multiplet, >C—CH=C<), 5.2 (multiplet, $>CH_2$=C—C<), 3.95 (multiplet, C=C—CH_2—O—), and 3.5 (multiplet, —O—CH_2C—O—) were 1.1:2:2.1:4.9, whereas initial ratios for AGE were 1:2:2.1:2.2, respectively].

In the run in which the AGE/HFA mole ratio was 1:1, and which gave a polymer with AGE/HFA ratio of 3:2, the loss of allylic and epoxy groups and formation of internal olefin were also indicated in the nmr. The relative band areas for δ 5.7, 5.2, 3.95, 3.5 were 1.4:2:2.6:4.9. The nmr spectrum also exhibited a broad multiplet, δ 2.4–3.0 (relative area *ca.* 1), which suggests >C=CH structures.

(55) W. F. Erman and T. J. Flautt, *J. Org. Chem.*, **27**, 1526 (1962).

(56) Runs were carried out on the Perkin-Elmer Model 154 with a stainless steel column length of 2 m, 0.25-in. o.d., packed with 20% fluoroalkyl pyromellitate on Gas Chrom R, 60–80 mesh. The helium flow rate was 10 cc/7.4 min; the vaporizer temperature was 210° and the column temperature 150°. Similar patterns were seen on silicon gum nitrile XL-60 on Gas Chrom R at a column temperature of 125° and a vaporizer temperature of 175°. The retention time, under the former conditions, was 10.45 min (98.0% of total) with the impurity at 8.3 min (1.5% of total).

(57) In the series CH_2=$CHCH_2C_7H_{15}$, CH_2=$CHCH_2OH$, CH_2=$CHCH_2NH_2$, and CH_2=$CHCH_2Br$, the chemical-shift values for the methynyl hydrogens are, respectively, δ 5.80, 6.0, 5.92, and 6.05 ppm.[53]

(58) Moderate.

Other characteristics of the latter run were 13 g of product obtained, mol wt 919 (ebullioscopic), and product insoluble in 5% NaOH. From the elemental analyses, the polymer contained 41, 42, and 38 mol % of HFA, respectively. Thus the product had an equivalent weight of 330–356, with an AGE/HFA mole ratio of 1.67–1.44 (3:2). The ir spectrum indicated relatively more OH (3.0 μ) and C–F (8.0 μ) content than in the first run.

Anal. Calcd for 3 mol of AGE/2 mol of HFA ($C_{24}H_{30}F_{12}O_8$): C, 42.7; H, 4.35; F, 33.8. Found: C, 42.54; H, 4.47; F, 31.98.

L. Terpolymerization of HFA with AGE and Phenyl Glycidyl Ether.—AGE (11.0 g, 0.1 mol), phenyl glycidyl ether (15.0 g, 0.1 mol), hydroquinone (0.01 g), and HFA (17 g, 0.1 mol) were allowed to react according to the procedure given in part A. The temperature was raised to 100° for 2 hr. A slow pressure drop was observed over this time period (40 psi → 30 psi). The temperature was raised to 115° for 3 hr more. This was accompanied by a further pressure drop to 15 psi. The tube was cooled and vented. Approximately 37 g of slightly viscous, light-colored liquid was obtained, which on distillation under nitrogen at reduced pressures in a platinum gauze-filled spinning-band still gave the following fractions: (1) 2.4 g, bp 40–70° (1.5–2.0 mm) (pot 90–100°, bath 120–140°); (2) 12.1 g, bp 70–78° (1 mm) (pot 120–150°, bath 150–158°); and (3) residue 15.5 g, very viscous, light amber liquid.

The residue was further heated in a rotating evaporator at 150° (1 mm) for 30 min. This residue (13 g) was still light amber, but was now a rather hard solid at room temperature. Its cryoscopic molecular weight (in benzene) was 1063. The infrared spectrum (5% in CCl_4) showed a weak, broad absorption band at 2.9–3.0 (associated —OH), a strong band at 8.1 (C—F), and moderately strong bands at 6.15, 6.60, 9.4 and 14.6 μ characteristic of the phenyl group. The band intensities of the latter corresponded to a 15% concentration by weight of phenyl glycidyl ether in the residue. Bands at 8.6 and 8.8 (strong) and 10.6 μ (weak, ether groups) were also present.

From the analyses, an average of 2.4 mol of HFA/1 mol of phenyl glycidyl ether/4 mol of AGE is present in the polymeric residue. The calculations from the elemental analyses alone, or per cent of fluorine plus infrared estimates of phenyl glycidyl ether content give minimum molecular weights which agree very well with each other and with the observed molecular weight (996 *vs.* 1006 *vs.* 1063).

Anal. Calcd for 2.5 mol of HFA/1 mol of PGE/4 mol of AGE ($C_{81}H_{100}F_{30}O_{25}$): C, 47.6; H, 4.9; F, 27.95. Found: C, 48.26; H, 4.74; F, 27.23.

M. Reaction of HFA with Octene-1 in the Presence of Phenyl Glycidyl Ether.—Octene-1 (11 g, 0.1 mol, Phillips Chemical Co., pure grade), phenyl glycidyl ether (distilled, 30 g, 0.2 mol), hydroquinone (0.01 g), and HFA (17 g, 0.1 mol) were allowed to react according to procedure A. The tube was held at 75° for 1 hr. The internal pressure reached 15 psi, and there was no pressure drop. The inside temperature was then raised to 100° for 2 hr. The gauge pressure fell to zero (atmospheric) within 1 hr. The tube was cooled and vented. The product was a clear, nonviscous liquid (51 g). The infrared spectrum of the crude product (5% in CCl_4) greatly resembled straight phenyl glycidyl ether, but with increased absorption at 2.9–3.0 and at 7.7 μ, indicating that some adduct was formed.

On distillation, the fractions were (1) 12.1 g, bp 35–53° (0.7 mm), almost all at 52–53° (0.7 mm); (2) 7.5 g, bp 53–71° (0.7 mm); (3) 20.7 g, bp 71–73° (0.6 mm); and (4) 1.6 g of residue, clear, nonviscous liquid.

The infrared spectrum of fraction 1 showed the bands expected for the HFA–octene adduct, *i.e.*, 2.8 (fairly weak, OH), 6.6, and doublets at 6.7, 6.8 (fairly weak, C=C), 8.0 8.6 (very strong, C—F), and 10.1, 10.6 (mod., —CH=CH—), and 14.1 μ (moderate, C—F). This fraction, although not redistilled to remove small amounts of low boiling material, gave an elemental analysis which supported this structure. The boiling point was in the expected range from the literature value for the 1-nonene–HFA adduct.[3]

Anal. Calcd for $C_{11}H_{16}F_6O$: C, 45.37; H, 5.99; F, 42.70. Found: C, 49.50; H, 5.90; F, 38.0.

The infrared spectra of fractions 3 and 4 were exactly those of phenyl glycidyl ether. Fraction 2 was a mixture of the adduct and phenyl glycidyl ether.

Thus about 27 of the original 30 g of phenyl glycidyl ether were recovered, and about 50% of the octene and HFA were converted into adduct. There was no evidence for secondary products which might result from reaction of the adduct with phenyl glycidyl ether.

N. Reaction of HFA with Styrene.—Styrene (64 g, 0.5 mol, Eastman White Label) and hydroquinone (0.01 g) were placed in the 300-cc bomb, and HFA (99 g, 0.6 mol) was added under nitrogen as in procedure A. Shaking was started below 0°, and the tube was then heated at 130° for 1 hr. An appreciable exotherm was observed during this period indicating a slow reaction, and the pressure rose to 370 psi. However, there was no pressure drop, which indicated a negligible reaction of the HFA. The internal temperature was then raised to 150° for 1 hr. Again an exotherm was evident, but again no pressure drop was observed (415 psi). The internal temperature was raised to 165° for 4 hr, and again the exotherm, but no pressure drop, was observed (450 psi). The tube was cooled, and 72 g of a stiff gel were removed. This gel was soluble in benzene, and slightly soluble in acetone. The product was treated with three successive 250-ml portions of acetone in an Osterizer, and the extracts were combined and distilled at 40–50 mm. About 10 g of styrene were recovered, bp 25° (40–50 mm). The distillation residue was dried in a vacuum oven at 70° for 14 hr. It was a gummy, tacky solid (2 g) with mol wt 629 (cryoscopic, benzene). The inherent viscosity (0.25% in benzene) was 0.023. The elemental analyses indicate 83–86 wt % styrene, or eight to nine molecules of styrene present for every molecule of HFA, and a formula weight of 894. The infrared spectrum showed bands at 2.8 (weak, —OH), 5.95 (C=C), and 8.2 and 8.6 μ (strong, C—F).

Anal. Calcd for $(C_8H_8)_8(C_3F_6O)$ or $C_{67}H_{64}F_6O$: C, 80.5; H, 6.5; F, 11.5. Found: C, 80.48; H, 6.58; F, 10.79.

The acetone-insoluble residue (59 g) was a stiff, brittle plastic.

Anal. Calcd (for polystyrene) C_8H_8: C, 92.3, H, 7.7. Found: C, 90.0; H, 7.6; F, 2.3.

After reprecipitation out of benzene with acetone in an Osterizer, the infrared spectrum was that of polystyrene, and the F content dropped to less than 0.4%. The ebullioscopic molecular weight in benzene was 6700 ± 700. Thus both fractions exhibited a lower molecular weight than calculated for one HFA end group (0.4% by weight of HFA per chain in the higher molecular weight fraction would lead to a molecular weight of *ca.* 25,000). This is a much higher chain-transfer level than is found in free-radical-initiated styrene polymerizations.

Registry No.—Adduct A, 646-97-9; adduct B, 15735-54-3; adduct C, 15735-55-4; adduct D, 15735-56-5; adduct G, 15735-57-6; adduct H, 15816-02-1; adduct J, 15735-58-7; HFA, 684-16-2; AGE, 106-92-3; phenyl glycidyl ether, 122-60-1; octene-1, 111-66-0; styrene, 100-42-5.

Acknowledgments.—The shaker tube reactions were run under the supervision of H. E. Cupery and the lvpc measurements were determined by Mrs. Adah B. Richmond. Valuable discussion was held with Dr. H. E. Simmons, Jr., of the Central Research Department, Du Pont.

The Question of Activation by the o-Nitro Group in Nucleophilic Aromatic Substitution[1]

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The reactivities in dimethyl sulfoxide of a series of amines (piperidine, 2-methylpiperidine, and *trans*-2,6-dimethylpiperidine) toward fluoro-2,4-dinitrobenzene or fluoro-2-nitrobenzene are reported and compared with those already reported for fluoro-4-nitrobenzene in the same solvent or chloro-2,4-dinitrobenzene in benzene. It is found that the piperidine:2-methylpiperidine:*trans*-2,6-dimethylpiperidine rate ratios are closely similar to one another in the four series of reactions (about $1:2 \times 10^{-3}:3 \times 10^{-5}$, respectively). Moroever, the *ortho*:*para* activation ratio varies little and randomly (from 0.86 to 2.0) upon changing the nucleophile. These facts are interpretable in terms of a nearly tetrahedral transition state in which steric inhibition of resonance of the *o*-nitro group is not pronounced. Therefore, the large drop in rate observed on introducing 2- or 6-methyl groups in the piperidine reagent must be attributed primarily to steric compression of the amine moiety against the benzene carbons and hydrogens in the transition state. The ultraviolet spectra show that steric inhibition of resonance is very marked for all reaction products of the 2-nitro series, varies widely from one member to another in the 2,4-dinitro series, and is absent from all members of the 4-nitro series. The lack of correlation of reaction rates and resonance stabilization of the reaction products is also explained.

A large amount of information is available concerning the activation by the nitro group in nucleophilic aromatic substitution.[3,4] Concerning the *ortho*:*para* activation ratio, the values found in the various reactions are thought[3] to reflect a fine balance among several factors which are recognized as (a) the inductive effect of the nitro group (whereby *ortho* activation is expected to prevail) and (b) proximity effects. Thus, an *ortho*:*para* ratio smaller than unity in reactions with anionic nucleophiles is attributed to inhibition of resonance of the *o*-nitro group in the transition state owing to steric repulsions[3] and to repulsions between like charges.[3,5] In the reactions with protic amines, where the *ortho*:*para* ratio is greater than unity, this effect is thought to be overwhelmed by that of hydrogen bonding[4a] between an ammonium proton and the *o*-nitro group in the transition state. The "hydrogen-bonding" idea has been tested experimentally,[6] while no systematic study concerned with the "steric" or with the "repulsions between like charges" idea has ever appeared.

In the course of related work on the reactivity of fluoro-4-nitrobenzene with piperidine, 2-methylpiperidine or *trans*-2,6-dimethylpiperidine in dimethyl sulfoxide (DMSO) we have recently discovered that, although the reactivity range spanned by the amines is greater than 10^4, the insertion of a second nitro group in the *ortho* position to the substrate (fluoro-2,4-dinitrobenzene) does not drastically alter the pattern of relative rates.[7] These results seemed to suggest[7] that there is no pronounced steric inhibition of resonance of the *o*-nitro group in the transition state.

However, the two series of reactions had been carried out in two different solvents, DMSO for fluoro-4-nitrobenzene[7] and benzene for fluoro-2,4-dinitrobenzene.[8] As the kinetics of reactions of this kind are dramatically altered on changing the solvent from DMSO to benzene (*vide infra*), it seemed of interest to investigate the reactivities of both fluoro-4-nitrobenzene and fluoro-2,4-dinitrobenzene in the same solvent. Moreover, in order to appraise directly the influences of the steric requirements of the nucleophile on the *ortho*:*para* activation ratio by the nitro group, we decided to investigate the reactivity of fluoro-2-nitrobenzene toward piperidine, 2-methylpiperidine, or *trans*-2,6-dimethylpiperidine.

It seemed also of interest to investigate whether a correlation between reaction rate and resonance stabilization of the reaction products, like that reported[9] for certain aromatic nucleophilic substitution reactions, holds for the present reactions as well. To this end the ultraviolet spectra of the reaction products were obtained and are utilized here as a criterion to qualitatively estimating resonance stabilization.

Results

The choice of DMSO as a solvent in which to compare the reactivities of our substrates was demanded by the fact that the reactions of fluoro-4-nitrobenzene with sterically hindered piperidines are too slow in benzene to be followed conveniently.[10] Moreover, while the displacement of fluorine from some fluoronitrobenzenes by protic amines displays complex kinetics,[11] this is not so in DMSO where clean second-order kinetics are observed.[12]

Rate data for the reactions of piperidine, 2-methylpiperidine, or *trans*-2,6-dimethylpiperidine with fluoro-

(1) Supported by Consiglio Nazionale delle Ricerche, Roma.

(2) To whom inquiries concerning this paper should be addressed.

(3) J. F. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.*, **77**, 5051 (1955).

(4) For recent contributions, see (a) S. D. Ross and M. Finkelstein, *J. Amer. Chem. Soc.*, **85**, 2603 (1963); (b) N. E. Sbarbati, *J. Org. Chem.*, **30**, 3365 (1965); (c) A. M. Porto, L. Altieri, A. J. Castro, and J. A. Brieux, *J. Chem. Soc., Ser. B*, 963 (1966); (d) J. Bourdon, D. Fisher, D. R. King, and J. C. Tatlow, *Chem. Comm.*, 65 (1965); (e) J. Bourdon, D. R. King, and J. C. Tatlow, *Tetrahedron*, **23**, 1347 (1967); (f) H. Suhr, *Ann.* **701**, 101 (1967). (g) C. W. L. Bevan, J. Hirst, and S. J. Una [*Nigerian J. Sci.*, **1**, 27 (1966)] are concerned with *meta* activation.

(5) M. F. Hawthorne, *J. Amer. Chem. Soc.*, **76**, 6358 (1954).

(6) Chlorine is displaced faster from chloro-4- than from chloro-2-nitrobenzene by a tertiary amine like triethylenediamine in benzyl alcohol[4a] whereas the reverse reactivity order is found when the nucleophile is a secondary amine like piperidine.[4a] Such an inversion of the reactivity order has been attributed to hydrogen bonding in the transition state for the reaction of the secondary amine with the *ortho*-substituted substrate. It is interesting, however, that chlorine is displaced much faster from chloro-2-nitrobenzene than from the *para* isomer by a nonprotic amine like pyridine in dimethyl sulfoxide.[4f]

(7) F. Pietra and F. Del Cima, *Tetrahedron Lett.*, 4453 (1966).

(8) F. Pietra and F. Del Cima, *ibid.*, 1925 (1966).

(9) F. Hawthorne and D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 5859 (1952).

(10) The reaction between fluoro-4-nitrobenzene 0.05 *M* and 2-methylpiperidine 0.9 *M* in benzene at 100° proceeded to only about 15% in 40 days.

(11) (a) F. Pietra and A. Fava, *Tetrahedron Lett.*, 1535 (1963); (b) F. Pietra and D. Vitali, *ibid.*, 5701 (1966).

(12) H. Suhr, *Ber. Bunsenges. Physik. Chem.*, **67**, 893 (1963).

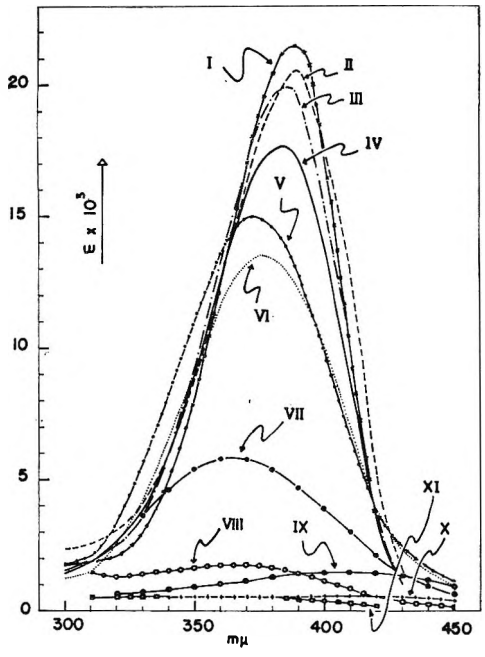

Figure 1.—The curves represent ultraviolet absorption spectra for the following compounds: I, N-4-nitrophenyl-*cis*-2,6-dimethylpiperidine; II, N-4-nitrophenyl-*trans*-2,6-dimethylpiperidine; III, N-4-nitrophenyl-2-methylpiperidine; IV, N-4-nitrophenylpiperidine; V, N-2,4-dinitrophenylpiperidine; VI, N-2,4-dinitrophenyl-2-methylpiperidine; VII, N-2,4-dinitrophenyl-*trans*-2,6-dimethylpiperidine; VIII, N-2,4-dinitrophenyl-*cis*-2,6-dimethylpiperidine; IX, N-2-nitrophenylpiperidine; X, N-2-nitrophenyl-2-methylpiperidine; XI, N-2-nitrophenyl-*trans*-2,6-dimethylpiperidine.

2,4-dinitrobenzene or fluoro-2-nitrobenzene in DMSO are reported in Table I. Formation of N-2,4-dinitro- or N-2-nitrophenylamines was quantitative (see the Experimental Section). Excellent kinetic plots were obtained up to 90% reaction completion in each case.

TABLE I

SECOND-ORDER RATE COEFFICIENTS FOR THE REACTIONS OF FLUORO-2,4-DINITROBENZENE OR FLUORO-2-NITROBENZENE WITH VARIOUS PIPERIDINES IN DMSO

Amine, *M*	Fluoro-2,4-dinitrobenzene, *M*	Fluoro-2-nitrobenzene, *M*	Temp, °C	k, mol^{-1} l. sec^{-1}
		Piperidine		
2.08×10^{-5}	9.8×10^{-6}		25	628
4.16×10^{-5}	1.96×10^{-5}		25	636
5.18×10^{-3}		3.11×10^{-4}	25	1.59×10^{-2}
3.26×10^{-2}		3.26×10^{-4}	25	1.61×10^{-2}
		2-Methylpiperidine		
4.90×10^{-4}	1.96×10^{-5}		25	0.64
1.17×10^{-3}	1.87×10^{-5}		25	0.69
0.791		5.40×10^{-2}	25	3.62×10^{-5}
0.500		5.30×10^{-2}	25	3.58×10^{-5}
		trans-2,6-Dimethylpiperidine		
1.42×10^{-2}	6.75×10^{-3}		25	0.010
3.34×10^{-2}	6.75×10^{-3}		25	0.012
0.397		7.00×10^{-2}	70	1.02×10^{-5}
0.589		7.25×10^{-2}	70	9.18×10^{-6}
0.589		7.25×10^{-2}	80	1.54×10^{-5}
0.589		7.25×10^{-2}	100	4.02×10^{-5}

Relative rates at a common temperature, and some activation parameters are reported in Table II for the substrates investigated here as well as for fluoro-4-nitrobenzene.[7] As the data for the latter compound were reported as a short communication,[7] some more experimental details are included in the Experimental Section for this compound as well.

The ultraviolet spectra of the N-substituted piperidines resulting from the reactions reported in Table II, together with those of N-4-nitrophenyl-*cis*-2,6-dimethylpiperidine,[7] and N-2,4-dinitrophenyl-*cis*-2,6-dimethylpiperidine,[8] are shown in Figure 1.

Discussion

Rate Data.—The reactions reported here are first order with respect to the amine, which means that there is no evidence for the existence of intermediates along the reaction path.[11,13] However, according to widely accepted ideas,[13] nucleophilic aromatic substitutions of this kind can be visualized as two-step processes in which formation of the intermediate is rate determining.

There are some interesting points to be noted from the data of Table II. (a) The reactivity range spanned by the three amines in the reactions with any single substrate encompasses a factor of more than 10^4 (columns 3, 7, and 11). (b) The patterns of relative rates for the reactions of each substrate with the three amines are fairly similar to one another (columns 3, 7, and 11). (c) The *ortho* : *para* activation ratio varies very little with changing amine (around unity) and without a definite trend. It is in fact 1.6, 2.0, and 0.86 for reactions with piperidine, 2-methylpiperidine, and *trans*-2,6-dimethylpiperidine, respectively (calculated from data in columns 2 and 6).

Finally, another interesting point emerges from the comparison of data of Table II with those already published.[8] (d) The pattern of relative rates found for the reactions of chloro-2,4-dinitrobenzene in benzene (1, 7.5 × 10^{-4}, and 4.7 × 10^{-6} for piperidine, 2-methylpiperidine, and *trans*-2,6-dimethylpiperidine, respectively)[8] is not drastically different from that pertaining to the corresponding reactions of fluoro-2,4-dinitrobenzene in DMSO (Table II).

Point a is a reflection of a large increase in steric compression in the transition state on increasing the bulk of the nucleophile. In fact, from an electronic point of view the substitution of methyl for hydrogen in the nucleophile should, if anything, increase the rate of reaction.

It is also clear that the above-discussed steric compression in the transition state cannot involve to any great extent the 2-nitro group. It is in fact easily recognizable that the trends observed in the rates (points b and c) cannot arise from a balance between steric compression involving the 2-nitro group in the transition state and such factors as (1) inductive effect being greater from the *ortho* than from the *para* position,[3] (2) inhibition of resonance of the 2-nitro group in the reagents,[3] and (3) "built-in-solvation."[3] Let us suppose in fact that steric compression involving the 2-nitro group in the transition state does increase steeply on going from piperidine to *trans*-2,6-dimethylpiperidine in the reactions of Table II. Then factors 1 and 2 cannot run in parallel opposition simply because they are independent of the nucleophile. There is no obvious reason, also, why the importance of "built-

(13) J. F. Bunnett and R. H. Garst, *J. Amer. Chem. Soc.*, **87**, 3875 (1965).

TABLE II

SECOND-ORDER RATE COEFFICIENTS, RELATIVE RATES (WITH RESPECT TO THE FASTEST AMINE FOR EACH SUBSTRATE), AND SOME ACTIVATION PARAMETERS FOR REACTIONS OF VARIOUS PIPERIDINES WITH NITRO-SUBSTITUTED FLUOROBENZENES IN DMSO AT 25°

	Fluoro-2-nitrobenzene				Fluoro-4-nitrobenzene[a]				Fluoro-2,4-dinitrobenzene	
Amine	k, mol^{-1} l. sec^{-1}	k_{rel}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	k, mol^{-1} l. sec^{-1}	k_{rel}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	k, mol^{-1} l. sec^{-1}	k_{rel}
Piperidine	1.60×10^{-2}	1			1.01×10^{-2}	1	8.0[b]	−43[b]	630	1
2-Methylpiperidine	3.60×10^{-5}	2.2×10^{-3}			1.76×10^{-5}	1.7×10^{-3}			0.65	1.0×10^{-3}
trans-2,6-Dimethylpiperidine	6.0×10^{-7}[c]	3.7×10^{-5}	12	−48	7×10^{-7}[c]	6.9×10^{-5}	11	−51	0.011	1.7×10^{-5}

[a] Data from ref 7. [b] Recalculated from rate data of ref 30. $\Delta S^{\ddagger} = -15.4$ eu, as reported in ref 30, is the result of a misprint or of an error in the calculation. [c] Extrapolated from data at higher temperatures.

in-solvation" should be augmented upon increasing the bulk of the nucleophile.[14]

Finally, consideration of point d suggests that the steric compression in the transition state of the reactions of Table II does not involve the leaving group to any considerable extent.

The above conclusions have been based on rate data at a single temperature. Systematic investigation of the temperature dependence of the rates has not been considered necessary because of the very wide ranges of reactivity spanned either by the nucleophiles with each substrate (point a) or by the substrates with respect to the same nucleophile [fluoro-2,4-dinitrobenzene is more than 10^4-fold faster than the other two substrates (Table II)]. Under such conditions a drastic change, due to temperature variation, of the trends observed among the data in Table II is conceivable only if the range of temperature covered is so wide that it may even be inaccessible experimentally in the solvent used (DMSO). On the other hand it may be noted that the reactions of *trans*-2,6-dimethylpiperidine with fluoro-2- or fluoro-4-nitrobenzene have similar activation parameters (Table II, lower row).

We are now in a position to draw some conclusions about the structure of the transition state for the reactions of Table II. The tetrahedral intermediate proposed by Bunnett[13] for aromatic nucleophilic substitution appears to be a good model for the transition state. In such a transition state repulsive interactions involving the 2-nitro group and the leaving group can be minimized as the 2-nitro group can adapt itself between the entering and the leaving group thus attaining coplanarity (or nearly so) with the benzene ring. The large drop in rate observed in the reactions of Table II on going from piperidine to 2-methylpiperidine and from this one to *trans*-2,6-dimethylpiperidine must then be attributed mainly to increased repulsive interactions between the nucleophile and the benzene ring carbons and hydrogens in the transition state.

The above observations are relevant to the problem, thus far little considered, of defining the conformation of the transition state. Thus, the present findings show that the preferred conformation of the transition state in the reactions of *o*-nitro-substituted substrates with all three amine reagents is one in which the piperidine carbons are turned away from the *o*-nitro group (if there is one as in the present case) and the ammonium hydrogen is turned toward *o*-nitro, available for hydrogen bonding. Thus, the various effects (inductive, hydrogen bonding, steric inhibition of resonance, etc.) of an *o*-nitro group can operate equally well with piperidine as with *trans*-2,6-dimethylpiperidine.

Whereas the present results obviously aid in clarifying why in the reactions of protic amines the *ortho*:*para* activation ratio is usually greater than unity, they have no very direct bearing on the question of what determines the *ortho* : *para* ratio in the reactions with alkoxide reagents.[3,4] This is due exactly to the fact that hydrogen bonding in the transition state holds the piperidine carbons away from the *o*-nitro group.

However, owing to the fact that *cis*-2,6-dimethylpiperidine is only six times less reactive than its *trans* isomer toward chloro-2,4-dinitrobenzene in benzene[8] (clearly, if the preferred conformation of the transition state is that pictured above, a methyl group must be closer to the *o*-nitro group in the case of the *cis*- than in that of the *trans*-amine) our results cast a little doubt[17] on the argument[3] that the difference in the *ortho*:*para* ratio, with methoxide or ethoxide reagents, between fluoro- and chloronitrobenzenes is attributable primarily to steric inhibition of resonance of the *o*-nitro group in the transition states of the reactions of *o*-chloronitrobenzenes.

Perhaps the importance of the "repulsions between like charges" idea[5] (see above) is even greater than was thought in the past.[3] However, even the latter idea alone is insufficient to rationalize consistently all the material published.

It is our opinion that a systematic investigation of reactions of anionic nucleophiles, in which steric effects are clearly defined, would be warranted.

Recently Crampton and Gold[18] and, independently, Servis[19] have discovered that, on mixing picryl methyl ether with methoxide in DMSO–methanol mixtures, addition of methoxide is faster to nuclear position 3 than to position 1, while the latter process gives the

(14) Factors 1 to 3 must also be of limited concern here. As for factor 1, it seems reasonable to assume that the inductive effect of the 2-nitro *vs.* that of the 4-nitro group is similar to that found in the case of 4- and 2-chlorine,[15] *i.e.*, only 7:1. Factor 2 is likely to be of little concern owing to the small size of fluorine.[16] In any event, the coplanar geometry is essential to the transition state, when the nitro group must accept electrons from the nucleophile, but not for the *o*-nitrophenyl halide molecule. Factor 3 must be of reduced importance owing to the high polarity of the solvent used (DMSO).[3]

(15) Data for chlorine are reported and discussed by J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 315 (1951).

(16) B. Capon and N. B. Chapmann, *J. Chem. Soc.*, 600 (1957).

(17) A prerequisite to our argument is, however, that the relative position of transition state and intermediate along the reaction coordinate is the same for reactions of both anionic and neutral nucleophiles. If Hawthorne's argument[5] is valid according to which the transition states for reactions of anionic nucleophiles is more reagentlike than those for reactions of neutral nucleophiles, our results have an even less direct bearing to the problem[3,4] of what determines the *ortho*:*para* ratio in the reactions of anionic nucleophiles.

(18) M. R. Crampton and V. Gold, *ibid.*, *Ser. B*, 893 (1966).

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

thermodynamically more stable product. Crampton and Gold[18] suggested that the slowness of the reaction at position 1 is due to steric compression in the transition state and wrote, "The implied importance of these steric effects suggests that Meisenheimer complexes themselves are unlikely to be good models for the transition state of nucleophilic aromatic substitution reactions for systems containing *o*-substituents." We must urge against acceptance of the above generalization.[18] In fact, our results, obtained for reactions of *ortho*-substituted compounds (with only one *ortho* group) in which steric effects are well defined, can be rationalized only if a nearly tetrahedral structure, like that attributed to Meisenheimer complexes, is assumed for the transition state.

Resonance Stabilization of the Reaction Products.—A qualitative estimate of the relative resonance stabilization among the reaction products of the reactions of Table II can be obtained by examination of the ultraviolet spectra in Figure 1.

These spectra clearly show that the three series of compounds (4-nitro, 2-nitro, and 2,4-dinitro) fall into three different classes. The 4-nitro series shares the common characteristic of having a high intensity band (ϵ) at λ_{max} 380–390 mμ. The intensity of absorption (ϵ) increases slightly, but consistently, on going from the less to the more bulky amine (Figure 1). In sharp contrast the 2-nitro series exhibits very low absorption in the region 300–450 mμ. Methyl and dimethyl compounds present the lowest intensity without a pronounced maximum of absorption (Figure 1). The features of the spectra belonging to the 2,4-dinitro series diverge from those of the other two series; here the intensity of absorption (ϵ) decreases steadily from a very high value for the piperidine derivative to a very low one for the *cis*-2,6-dimethylpiperidine compound (Figure 1).

The spectra of the 4-nitro series in benzene (Figure 1) resemble closely those of 4-nitroaniline[20] and of its N-methyl and N-ethyl derivatives[20] in ethanol. Therefore, steric inhibition of ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) resonance, which has been excluded for the last compounds,[20] should also be absent from all the N-4-nitrophenylpiperidines of Figure 1.[21,22]

The very low absorptions of the compounds belonging to the 2-nitro series, compared with those of the 4-nitro series (Figure 1), cannot be attributed only to the shorter transition moments in the former series. In fact 2-nitroaniline exhibits a definite absorption band in ethanol which is much stronger (ϵ 5.2 $\times$ 10^3, λ_{max} 404 mμ)[20] than that of any of the 2-nitro amines of Figure 1. The logical conclusion[21] is that in the series of N-2-nitrophenylpiperidines of Figure 1 there is pronounced steric inhibition of ($>^+N{=}C_1 \rightarrow C_2{=}NO_2^-$) resonance. It seems also reasonable to assume that steric strain is relieved by rotation from planarity of both the $C_5H_{10}N-$ and the $-NO_2$ group. The latter point is appreciated more clearly by examination of the spectra of the compounds of the 2,4-dinitro series (Figure 1). According to the results obtained for 2,4-dinitroaniline and its N-methyl and N-ethyl derivatives,[20] the absorption band of Figure 1 for N-2,4-dinitrophenylpiperidine should be assigned to the ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) transition, while ($>^+N{=}C_1 \rightarrow C_2{=}NO_2^-$) resonance should be sterically inhibited. In fact, not even an inflection marks the position of the ($>^+N{=}C_1 \rightarrow C_2{=}NO_2^-$) transition in the spectrum of N-2,4-dinitrophenylpiperidine (Figure 1). Moreover, as band half-widths at half-height are about equal on both sides of the maximum of absorption (Figure 1), overlapping of absorption on the longer wave length side due to the ($>^+N{=}C_1 \rightarrow C_2{=}NO_2^-$) transition can be excluded. These findings suggest then that the 2-nitro group is completely out of the plane of the benzene ring in N-2,4-dinitrophenylpiperidine.

It is also of interest that a change from 2,4-dinitroaniline to its N,N-dimethyl or N,N-diethyl derivatives results in steric enhancement of ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) resonance,[20] as evidenced by the increase in the absorption attributed to the ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) electronic transition.[20] Here, on the contrary, going from N-2,4-dinitrophenylpiperidine to its dimethyl (*trans* or *cis*) derivatives produces pronounced steric inhibition of ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) resonance. In fact, a sharp decrease of intensity of absorption (ϵ) is observed on going from N-2,4-dinitrophenylpiperidine to its dimethyl (*trans* or *cis*) derivatives (Figure 1). A likely explanation is that in the cases of N-2,4-dinitrophenyl-*cis*-2,6-dimethylpiperidine or of its isomer the amino moiety has such large steric requirements that, besides rotating the *o*-nitro group out of the plane of the benzene ring, it is itself rotated from planarity. That the *o*-nitro group is sterically involved in inhibiting conjugation of the amino nitrogen in the latter compounds is also shown by the fact that in the 4-nitro series (Figure 1) there is no steric inhibition of ($>^+N{=}C_1 \rightarrow C_4{=}NO_2^-$) resonance.

Lack of Correlation of Reaction Rate and Resonance Stabilization of the Reaction Products.—Hawthorne and Cram have studied[9] the competitive reaction of L-(+)-α-phenylethylamine with DL-2-(*sec*-butyl)-4,6-dinitrochlorobenzene to give (−)-DL-2-(*sec*-butyl)-4,6-dinitro-N-(L-α-phenylethyl)aniline and the (+)-LL diastereomer. The latter diastereomer is slightly more stabilized by resonance (as judged from ultraviolet spectra) and is formed 1.22 times as fast as the former one.[9]

Such a correlation apparently does not hold for the reactions investigated in the present work. As shown above, while steric inhibition of resonance is absent in all reaction products of the 4-nitro series and increases markedly in the other two (2-nitro and 2,4-dinitro) on increasing the bulk around the amino nitrogen in the nucleophile, we have found that the patterns of relative rates (encompassing a factor greater than 10^4) in the three series of reactions are similar to one another. Moreover, the *ortho* : *para* ratio varies little and without any definite trend.

It can be argued that this apparent disagreement is due to the fact that in Cram's work[9] two *ortho* substituents are present, one of which has a tetrahedral geometry. Thus, while the steric interactions in the

(20) M. J. Kamlet, H. G. Adolph, and J. C. Hoffsommer, *J. Amer. Chem. Soc.*, **86**, 4018 (1964).

(21) We are aware of the ultraviolet spectral changes that *p*-nitroanilines undergo on changing from a nonpolar aprotic solvent like carbon tetrachloride to ethanol.[22] However, such changes are small enough that, for the present purposes, we can safely compare our ultraviolet spectra in benzene with others in ethanol.

(22) (a) J. H. P. Utley, *J. Chem. Soc.*, 3252 (1963); (b) M. J. Kamlet, *Israel J. Chem.*, **1**, 428 (1963).

reaction products can be released in the transition state owing to the favorable geometry of the nitro group (our case), this is not possible in the reactions studied by Cram.[9] In the tetrahedral transition state of these reactions the ammonium proton is turned toward the *o*-nitro group, which probably does not undergo steric inhibition of resonance, while the 2-*sec*-butyl group, also due to its tetrahedral geometry, must interfere sterically with the entering group even in the transition state.

Perhaps the results of our work suggest that the subtle difference between the rates of the reactions studied by Cram[9] originates from steric repulsions in the transition state involving the entering group and the 2-*sec*-butyl group at a greater extent than the 2-nitro group. This is an interesting question that remained thus far unsolved (see the discussion by Hammond and Hawthorne).[23]

Experimental Section

Melting points were taken on a Kofler apparatus and are uncorrected.

Materials. **DMSO** (Erba) was fractionally distilled (N_2 atmosphere, column as described below for 2-methylpiperidine, 20 mm, reflux ratio 8°1). Central cuts were collected and redistilled at 20 mm over calcium hydride (N_2 atmosphere) before use. **Fluoro-2-nitrobenzene** (Fluka) was fractionally distilled (18 mm, N_2 atmosphere). Fractions containing less than 0.1% total impurities (vpc,[24] Apiezon on Chromosorb W 80–100 mesh, 135°, retention time 7 min) were used. **Fluoro-4-nitrobenzene** (Schuchardt) and **fluoro-2,4-dinitrobenzene** (Fluka) were recrystallized several times from absolute ethanol. Piperidine (Erba) was refluxed over sodium metal for several hours and then distilled under an N_2 atmosphere. Fractions containing less than 0.1% total impurities (vpc,[24] 20% 1-hydroxyethyl 2-heptadecenyl glyoxalidine on 60–80 mesh KOH-washed Chromosorb W, 80°) were used. Commercial **2-methylpiperidine** (Eastman, White Label) was fractionally distilled under N_2 atmosphere (column 3 ft × 3/5 in. packed with Fenske glass helices 1/10 in. and equipped with a thermostated jacket, 100 mm, 60°, reflux ratio 35:1) and redistilled under reduced pressure over Na–K alloy before use. After this treatment, vpc[24] (column as before for piperidine, 88°) did not show any contamination. *trans*-2,6-Dimethylpiperidine after three fractional distillations under the conditions already reported[8] (reflux ratio 40:1) did not show any contamination (retention times in vpc,[24] under the conditions already reported,[8] were 15 and 10 min for the *trans* and the *cis* isomer, respectively). **N-2-Nitrophenylpiperidine**, mp 78° (lit.[25] 81°), **N-4-nitrophenylpiperidine**, mp 103–104° (lit.[25] 105.5°), **N-2,4-dinitrophenylpiperidine**, mp 95–95.5° (lit.[25] 92°), and **N-2,4-dinitrophenyl-2-methylpiperidine**, mp 72–73° (lit.[26] 67°), were prepared by standard procedures. **N-2,4-Dinitrophenyl-*trans*-2,6-dimethylpiperidine** and its *cis* isomer were those used in a previous work.[8]

N-2-Nitrophenyl-2-methylpiperidine, obtained as orange needles, mp 27–27.5° (lit.[27] 75°), picrate mp 142–143 from ethanol (lit.[27] 141–142°), was prepared by the reaction of fluoro-2-nitrobenzene with 2-methylpiperidine. The pure materials (in a molar ratio of 1:2 of fluoro compound over amine) were sealed in a pyrex tube and heated at 100° for seven days. Then the reaction mixture was poured into ice water and a red-brown viscous oil was separated. Plc[28] (benzene) of this material showed a yellow band at R_f 0.8 which gave yellow crystals the melting point of which did not rise over 27–27.5° after several recrystallizations from petroleum ether (30–50°). The yield was 75%. The same material was obtained in 80% yield from the reaction of the same reagents in DMSO (fluoro compound 0.1 *M*, amine 1.4 *M*, temperature 25°, reaction time 5 days). The pmr spectrum[29] supported the proposed structure showing absorption attributed to the three-proton (doublet, δ 0.87, J = 6 cps) of the methyl group, the six-proton (broad absorption, centered at δ 1.6) of both the β- and the δ-methylene groups, the three-proton (complex pattern, δ 2.4–3.4) of both the α-methylene and the methine groups, and the four-proton (complex pattern centered at δ 7.25) of the aromatic ring. *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.4; H, 7.3; N, 12.7. Found: C, 65.5; H, 7.6; N, 12.7.

N-2-Nitrophenyl-*trans*-2,6-dimethylpiperidine was prepared by the reaction of fluoro-2-nitrobenzene with *trans*-2,6-dimethylpiperidine. The two reagents (in a molar ratio 1:2 of fluoro compound over amine) were sealed in a pyrex tube and heated at 100° for 5 days. The reaction mixture was then poured into ice water and the solid that separated out was purified by plc[28] (benzene). The yellow band at R_f 0.8 gave orange crystals which, after recrystallization from petroleum ether (30–50°), melted at 52.5–53.5°. The yield was 70%. The pmr spectrum[29] supported the proposed structure showing absorption attributed to the six-proton (doublet δ 0.90, J = 6.5 cps) of the methyl groups, the six-proton (broad absorption centered at δ 1.6) of the methylene groups, the two-proton (broad absorption centered at δ 3.4) of the methine groups, and the four-proton (complex pattern δ 6.9–7.6) of the aromatic ring. *Anal.* Calcd for $C_{13}H_{18}N_2O_2$: C, 66.6; H, 7.7; N, 11.9. Found: C, 66.7; H, 7.8; N, 11.9.

N-4-Nitrophenyl-2-methylpiperidine, mp 61.5–62.5° (lit.[30] 59.5–60.0), was prepared by the reaction of fluoro-4-nitrobenzene with 2-methylpiperidine by the last method above. Recrystallization from methanol gave yellow crystals (yield 85%) which did not show a sharp melting point. However, the pmr spectrum[29] of this material remained unchanged after sublimation at 50° (5×10^{-4} mm) and afforded yellow crystals with a sharp melting point (61.5–62.5°). The pmr spectrum[29] supported the proposed structure showing absorption attributed to the three-proton (doublet, δ 1.2, J = 6.3 cps) of the methyl group, the six-proton (broad absorption centered at δ 1.7) of both the β- and the δ-methylene groups, the three-proton (complex pattern, δ 2.8–4.4) of both the α-methylene and the methine groups, and the four-proton (A_2X_2 system,[31] δ_A 8.07, δ_X 6.74, J_{AX} = 9.3 cps) of the aromatic ring. *Anal.* Calcd for $C_{12}H_{16}N_2O_2$: C, 65.4; H, 7.3; N, 12.7. Found: C, 65.5; H, 7.5; N, 12.6. Only a few details were reported about the preparation of **N-4-nitrophenyl-*cis*-2,6-dimethylpiperidine**.[7] We add now that the solvent, dry DMSO, and unreacted amine were removed *in vacuo* at 100° after reaction. The remaining yellow solid showed three yellow bands on plc[28] (glacial acetic acid) at R_f 0.1, 0.4, and 0.9. Band R_f 0.1 corresponded to the compound mentioned above, mp 147–149°. In the pmr spectrum[29] the A_2X_2 system,[31] attributed to the aromatic protons is characterized by δ_A 8.05, δ_X 6.69, and J_{AX} = 9.6 cps. The proposed structure is now fully supported by double resonance experiments which show that the absorption at δ 1.81[7] is attributable to the methylene groups. Thus, the broad absorption at δ 4.21[7] becomes a well-defined quartet attributable to a methine coupled with a methyl group (J = 6.3 cps) on irradiation at δ 1.81.

Kinetics.—The reaction kinetics were followed by measuring the increase in absorbance at the absorption maximum (Figure 1) of N-4-nitro-, N-2-nitro-, or N-2,4-dinitrophenylamines (406 and 350 mμ for N-2-nitrophenyl-2-methylpiperidine and N-2-nitrophenyl-*trans*-2,6-dimethylpiperidine, respectively). A Beckman DU spectrophotometer equipped with a thermostated cell compartment was used. At the chosen wavelengths, the absorption due to both the reagents and other reaction products was negligible. Beer's law plots were determined at the absorption maximum of each compound (in benzene–DMSO mixtures for the N-4-nitro- and N-2-nitro series; in DMSO for the other one). Straight lines passing through the origin were obtained in all cases (up to 6×10^{-4} *M* compounds, which was the highest

(23) G. S. Hammond and M. F. Hawthorne in "Steric Effects in Organic Chemistry," M. S. Newmann, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 195.

(24) A Perkin-Elmer Model 810 gas chromatograph with 6 ft × 1/8 in. columns, a flame-ionization detector, and a flow rate of 25 cc of N_2/min was used.

(25) E. Lellmann and W. Geller, *Ber.*, **21**, 2281 (1888).

(26) O. L. Brady and F. R. Cropper, *J. Chem. Soc.*, 507 (1950).

(27) O. Meth-Cohn, R. K. Smalley, and H. Suschitzky, *ibid.*, 1666 (1963).

(28) Preparative layer chromatography was carried out over a 2-mm-thick silica gel layer activated at 110° for 1 hr.

(29) A Varian nmr spectrometer Model DA-60IL was used. Determinations were run on 10% solutions in $CDCl_3$ with TMS as an internal standard at 28°.

(30) H. Suhr, *Ann.*, **689**, 109 (1965).

(31) As the internal chemical shift exceeds 30 cps, the A_2X_2 system ("A" refers to the protons in *ortho* position to the nitro group) can be adequately described by first-order analysis. See J. Martin and B. P. Dailey *J. Chem. Phys.*, **37**, 2594 (1962).

concentration used). In all cases the absorption spectrum (over the 300–450-mμ range) of the reaction mixture after several half-lives corresponded within 2% to the "mock" infinity prepared by the appropriate N-nitrophenylamine. To achieve this result it was necessary to exercise extreme care in the purification of the reacting amines. This was essential in the reactions of fluoro-2-nitrobenzene or fluoro-2,4-dinitrobenzene with excess of the more bulky amines. Thus, if less hindered amines were present as impurities, the experimental infinity was substantially higher than the "mock" one. This is because the less hindered amines are more reactive (Table II) and give final products with higher molar absorbance (Figure 1).

In the case of slow reactions, samples of the reaction mixture were sealed under nitrogen into Pyrex tubes which were then placed at the desired temperature and cooled at room temperature; the content was diluted (50- to 2500-fold) with benzene and immediately transferred into a stoppered cuvette for the spectral analysis (the absorbance was determined against that of benzene–DMSO solutions of the same composition; 10-mm matched quartz cuvettes were used). The combined processes of cooling and diluting the sample with benzene practically stopped the reaction. In the case of more rapid reactions, carried out at 25°, the solutions of the two reagents were mixed and then samples of the reaction mixture were withdrawn at time intervals by means of a pipet in an atmosphere of dry N_2 and diluted with benzene as above. In the case of very rapid reactions, 100–300 μl of the appropriate amine solution was added to 3 ml of the solution of the appropriate fluoronitro compound contained in a 10-mm stoppered quartz cuvette in the spectrophotometer cell compartment. In this instance mixing was ensured by stirring the solution while adding the amine and, when possible, by vigorously shaking the cuvette after the process of mixing the reagents. The reverse process of adding 100–300 μl of the solution of fluoronitro compound to 3 ml of the amine solution gave the same rate values.

Rate coefficients were calculated by first-order plots when a large excess of amine was used, and by second-order plots in other cases. The stoichiometry used in the calculations was, in all cases, that shown by the equation below for the reaction of fluoro-2,4-dinitrobenzene with piperidine.

$$(O_2N)_2C_6H_3F + 2C_5H_{10}NH = (O_2N)_2C_6H_3NC_5H_{10} + C_5H_{10}NH_2^+F^-$$

Ultraviolet Spectra.—Ultraviolet spectra over the range 300–450 mμ were determined in benzene solutions (Figure 1) using a Beckman DU spectrophotometer with matched 10-mm, stoppered quartz cuvettes. Concentration never exceeded 4×10^{-4} *M* (Beer's law was obeyed in benzene as well).

Registry No.—I, 15822-69-2; II, 15822-70-5; III, 15822-71-6; IV, 6574-15-8; V, 839-93-0; VI, 15822-74-9; VII, 15889-61-9; VIII, 15822-76-1; IX, 15822-77-2; X, 15822-78-3; XI, 15822-79-4.

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Homolytic Decompositions of Hydroperoxides. I.[1] Summary and Implications for Autoxidation

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This paper summarizes and integrates the conclusions of the four succeeding papers which present experimental details on decompositions of hydroperoxides. Purely thermal decompositions by homolysis to alkoxy and hydroxy radicals have been experimentally approached but never fully attained. All decompositions of hydroperoxides are induced to a greater or lesser degree by metals or other sources of free radicals. The induced reactions are simple in principle; they depend mostly on competitions between nonterminating and terminating interactions of peroxy radicals (eq 3 and 4 below), competitions among two hydrogen abstractions by alkoxy radicals (from hydroperoxides or from reactive solvents in eq 2 and 9), and cleavage of alkoxy radicals by eq 7. These competitions depend on the hydroperoxide, solvent, and temperature. Decompositions induced by catalytic quantities of several metal salts are similar except for the participation of both metal and hydroperoxide in radical production. The complex kinetics of metal-catalyzed decompositions are ascribed to extensive association of metal salts and soaps in organic solvents and the constantly changing coordination of oxygen-containing compounds with the metals as the decompositions progress.

Traditionally, thermal decompositions of hydroperoxides, metal ion catalyzed decompositions, and decompositions by free-radical initiators have been treated as separate phenomena; yet all of these involve hydroperoxides in the presence of free radicals and are subject, to some extent,[3–5] to a concomitant radical-induced chain decomposition. The nature of this induced chain has been elucidated previously for simple cases.[6–8] This series of papers explains more complex aspects of this chain decomposition and shows how it operates as a unifying factor for all homolytic decompositions of hydroperoxides.

This report summarizes conclusions based on our own investigations and those of previous workers, and suggests some of their applications for autoxidations of hydrocarbons.

Free-Radical-Induced Decompositions

Background.—Hydroperoxides of all types are particularly labile toward attack by free radicals. An understanding of this destructive process, which is basic to our investigation, is facilitated if the initiating radicals are not generated by the hydroperoxides themselves. Decompositions of *t*-BuO_2H in benzene or chlorobenzene at 20–60°, initiated by di-*t*-butylperoxy oxalate (DBPO),[4,5] 2,2′-azobis(2-methylpropionitrile) (ABN),[9] and photolysis of hypochlorites[5] have elucidated a general mechanism. In the simplest instance,

(1) Parts II–V: R. Hiatt, *et al.*, *J. Org. Chem.*, **33**, 1421, 1428, 1430, 1436 (1968). Equations are numbered consecutively in papers I–V.

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(3) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p 504.

(4) S. W. Benson, *J. Chem. Phys.*, **40**, 1007 (1964).

(5) W. H. Richardson, *J. Amer. Chem. Soc.*, **87**, 1096 (1965).

(6) R. Hiatt, J. Clipsham, and T. Visser, *Can. J. Chem.*, **42**, 2754 (1964).

(7) D. B. Denny and J. D. Rosen, *Tetrahedron*, **20**, 1137 (1962).

(8) A. Factor, C. A. Russell, and T. G. Traylor, *J. Amer. Chem. Soc.*, **87**, 3692 (1965).

(9) J. R. Thomas, *ibid.*, **87**, 3935 (1965).

where initiator generates an alkoxy radical directly (R is often, but not necessarily, t-Bu·), eq 1–5 apply.

$$\text{DBPO} \longrightarrow 2\text{RO}\cdot + 2\text{CO}_2$$
$$R_i = \text{rate of initiation} = 2k_1[\text{DBPO}] \quad (1)$$

$$\text{RO}\cdot + \text{RO}_2\text{H} \longrightarrow \text{ROH} + \text{RO}_2\cdot \quad (2)$$

$$2\text{RO}_2\cdot \longrightarrow 2\text{RO}\cdot + \text{O}_2 \quad (3)$$

$$2\text{RO}_2\cdot \longrightarrow \text{RO}_2\text{R} + \text{O}_2 \quad (4)$$

$$-\text{d}[\text{RO}_2\text{H}]/\text{d}t = 2k_1[\text{DBPO}](1 + k_3/k_4) = R_i(1 + k_3/k_4) \quad (5)$$

Under the conditions specified above, the chain length (equal to $1 + k_3/k_4$) is about 11. However, in other solvents or with other tertiary hydroperoxides, the reaction appears to be much more complex.[10] For nontertiary hydroperoxides, a quite different mechanism has been proposed[11] (eq 6) analogous to the base-

$$\text{R}_1\text{R}_2\text{HCO}_2\text{H} + \cdot\text{OH} \longrightarrow \text{H}_2\text{O} + \text{R}_1\text{R}_2\text{CO}_2\text{H} \longrightarrow \text{R}_1\text{R}_2\text{C}{=}\text{O} + \cdot\text{OH} + \text{H}_2\text{O} \quad (6)$$

catalyzed decomposition.[12] Our own investigations are reported in parts II and III.[1]

t-Butyl hydroperoxide was decomposed at 100° in the gas phase or in benzene by radicals generated from t-Bu_2O_2 or sec-Bu_2O_2. Decompositions initiated by DBPO were carried out in acetic acid, t-butyl alcohol, and Nujol at 35–45° and also in refluxing n-heptane, cyclohexane, and n-pentane. Decompositions of primary and secondary hydroperoxides by DBPO were carried out at 45° in benzene.

Tertiary Hydroperoxides. The Viscosity of the Medium.—The chain length for radical-induced decomposition, according to eq 3–6, depends on the ratio of nonterminating to terminating interactions of peroxy radicals (k_3/k_4). If the initial result of interaction of two peroxy radicals is a pair of alkoxy radicals (+ oxygen) in a solvent cage, the ratio k_3/k_4 is controlled by the rate of diffusion out of the cage, and should be inversely proportional to the viscosity of the solvent. The expected relationship was observed for chain lengths of t-BuO_2H decompositions in benzene at 25–100°, a 2.5-fold change in solvent viscosity corresponding to an apparent activation energy of 2.3 kcal/mol for diffusion. Chain lengths as high as 50 (in the gas phase at 100°) and as low as 1 (in Nujol at 35°) were found. However, other factors also affect chain lengths.

Cleavage of Alkoxy Radicals.—Decomposition of t-BuO_2H at 100° in benzene, carbon tetrachloride, or gas phase, or at 45° in t-butyl alcohol or acetic acid did not obey the simple rate expression of eq 5 when the initial concentration of t-BuO_2H was less than 0.2 M (as it was for most measurements). Over-all chain lengths (here dependent on [t-BuO_2H]) as low as 1.5 were found and products included up to 27% acetone. Yields of oxygen, where measured, were as low as 25% of theory.

These differences between theory and experiment are due to cleavage of t-butoxy radicals (eq 7). As

$$t\text{-BuO}\cdot \longrightarrow \text{CH}_3\text{COCH}_3 + \text{CH}_3\cdot \quad (7)$$

Walling and Wagner[13] have shown, cleavage is favored in protic solvents over H abstractions such as reaction 2. Cleavage of t-BuO· becomes competitive at low [t-BuO_2H], even in benzene at higher temperatures, and then oxygen is partly scavenged by methyl radicals. Participation of $\text{CH}_3\cdot$ or $\text{CH}_3\text{O}_2\cdot$ in rapid termination reactions reduces chain lengths. When cleavage is the rate-determining step for termination, eq 8 applies. Experimentally determined rate laws

$$-\text{d}[\text{RO}_2\text{H}]/\text{d}t = R_ik_2[t\text{-BuO}_2\text{H}]/2k_7 \quad (8)$$

for less than 0.2 M t-BuO_2H at 100° (excepting those in the gas phase) closely approximate eq 8.

Protection of Hydroperoxides from Radical Attack.—Decompositions in alkanes, refluxed to expel oxygen, had chain lengths lower than corresponding runs in benzene, although alkoxy cleavage and yields of acetone were minimal. The maximum effect occurred in refluxing n-heptane where t-BuO_2H appeared to be untouched by initiating radicals. Similar effects were observed in the gas phase on addition of cyclopentene or isobutane vapor. The results are readily explained as increasing competition for RO· by solvent (SH) (eq 9) and the rapid terminations available to S·

$$\text{RO}\cdot + \text{SH} \longrightarrow \text{ROH} + \text{S}\cdot \quad (9)$$

(eq 10). Substantial quantities of the mixed peroxide

$$\text{S}\cdot + \text{RO}_2\cdot \longrightarrow \text{SO}_2\text{R} \quad (10)$$

SO_2R were isolated from products of decomposition in refluxing cyclohexane. Alkanes did not exert a protective effect at 170° probably because the mixed peroxides thermally decompose at that temperature.

Decompositions in the Gas Phase.—In the absence of added free-radical initiators, 3–27% t-BuO_2H decomposed in the gas phase at 100° in 15 hr, the time ordinarily used for induced decompositions. The lowest values were obtained using new or base-washed vessels. This surface-catalyzed reaction was thought to contribute about 10% to the total decomposition in ordinary vessels with added radical initiators, but was too erratic for meaningful corrections to be made. The rate expression for homogeneous induced decompositions is given in eq. 11. This relation cor-

$$-\text{d}[t\text{-BuO}_2\text{H}]/\text{d}t = k(R_i)^{1/2}[t\text{-BuO}_2\text{H}]^{1/2-1} \quad (11)$$

responds for unit order in [t-BuO_2H] to the expression expected for the chain decomposition if termination results only from random combination of alkoxy radicals. When decomposition was induced by sec-Bu_2O_2, no significant amount of t-Bu_2O_2 was found in the products, suggesting that MeO· or MeO_2· was involved in most terminations. Other products included 1–10% acetone, 90–95% t-BuOH, and 30–50% of the theoretical amount of O_2.

Primary and Secondary Hydroperoxides.—Decompositions of sec-butyl hydroperoxide by DBPO in benzene had a chain length of 1.0 at 45° and yielded about 50% each of sec-butyl alcohol and methyl ethyl ketone. At 100°, some acetaldehyde and acetic acid also appeared. Where measured at 45°, oxygen yields were 75–80% of theory. We interpret these results to mean that induced decompositions of nontertiary

(10) In neat t-BuO_2H, decomposition by DBPO had a gradually decreasing chain length, nearing 1 at 50% conversion: P. D. Bartlett, private communication, 1964.

(11) A. Robertson and W. A. Waters, *J. Chem. Soc.*, 1578 (1948).

(12) A. G. Davies, "Organic Peroxides," Butterworth and Co. Ltd., London, 1961, p 183.

(13) C. Walling and P. J. Wagner, *J. Amer. Chem. Soc.*, **86**, 3368 (1964).

hydroperoxides at 45° differ from those of t-BuO_2H only in that the interaction of two primary or secondary peroxy radicals almost always terminates the chain.

$$2R_1R_2HCO_2\cdot \longrightarrow [?] \longrightarrow R_1R_2HCOH + R_1R_2C{=}O + O_2 \quad (12)$$

We do not know what happens in the solvent cage, but believe that free alkoxy radicals are not formed there (part III[1]). Results from metal-catalyzed decompositions of *sec*-BuO_2H at 45° indicate that two *sec*-$BuO_2\cdot$ radicals yield *sec*-Bu_2O_2 about 3% of the time.

DBPO-induced decompositions of *n*-butyl, tetralyl, and cyclopentenyl hydroperoxides at 45° had over-all chain lengths of 0.6–0.7. For *n*-BuO_2H this probably resulted from some radical attack on the PrCHO produced from hydroperoxide decomposition. For the others, abstraction of allylic, rather than hydroperoxidic, H may have constituted terminating, chain-shortening reactions.

In benzene at 100° *sec*-butyl hydroperoxide was decomposed by *t*-butoxy radicals, producing variable amounts of ketone and alcohol and very little oxygen. This reaction probably involved attack at both the indicated bonds in $H(Me)CO_2(Et)H$ by alkylperoxy or alkoxy radicals as well as induced oxidations. Studies of this reaction are continuing. Much of the difference between the 45 and 100° results seems to be due to differences in rate of production of initiating t-$BuO\cdot$ radicals (part III[1]). Above 100°, primary and secondary hydroperoxides seem to have undergone radical-induced decompositions[4] with longer chain lengths (part V[1]).

Results of induced decompositions of *sec*-BuO_2H in the gas phase at 100° were complicated by surface-catalyzed decompositions of the hydroperoxide (part III[1]).

Implications for Autoxidations.—This section considers the implications of parts II and III[1] for the oxidation of hydrocarbons, first with respect to making and keeping hydroperoxides as primary oxidation products and then with respect to rates of oxidation as a function of structure. The generalizations below apply to alkanes and alkylbenzenes. They are tentative and subject to later revision. Our experience with allylic hydroperoxides is too limited to include alkenes in this discussion.

The preparation of hydroperoxides by autoxidation depends on a balance between closely related chain reactions. High concentrations of alkanes not only assist synthesis but retard decomposition. With alkanes the maximum protective effect is found at about 100°; with alkylbenzenes it is found at lower temperatures. Kinetic chain lengths for both synthesis and decomposition are greatest for t-alkyl hydroperoxides under conditions where little cleavage of alkoxy radicals occurs. Chain lengths are shortest with primary and secondary hydroperoxides because of the high activity of the corresponding peroxy radicals in chain termination.

In oxidations of hydrocarbons, reactions of peroxy radicals with substrate are desirable and chain terminations should be minimized. Three sets of competing reactions are therefore crucial. The first competition is between the reaction of peroxy radicals with hydrocarbon (to give hydroperoxide) and their reactions with each other (to give alkoxy radicals or cleavage products or chain termination). This choice can be controlled by the concentration of hydrocarbon and the rate of chain initiation, but usually the rate of initiation has to be higher than otherwise desirable to obtain a useful rate of reaction.

The other two sets of competing reactions correspond to the two competitions discussed above. Interaction of peroxy radicals may be terminating or nonterminating (eq 3 and 4) and the alkoxy radicals may cleave or react with hydrocarbon (eq 7 and 9). t-Butoxy radicals are the most stable t-alkoxy radicals toward cleavage[14-16] and so all other branched hydrocarbons will give more cleavage effects than isobutane.

These considerations indicate that in oxidations of hydrocarbons to hydroperoxides the longest kinetic chains will be obtained when attack on the tertiary hydrogen atoms is maximized and cleavage of any tertiary hydrogen atoms is maximized and cleavage of any tertiary alkoxy radicals is minimized. When secondary (or primary) hydrogen atoms are involved in oxidation in solution, long chains can be obtained only with very reactive C–H bonds (fast propagation) or low rates of chain initiation (minimum chain termination). Our results admit the possibility that the last restriction may not apply in gas phase oxidations if the terminating efficiency in interactions of secondary alkylperoxy radicals proves to be low.

Except where these restrictions can be avoided, most commercial oxidations must be short-chain processes in which fairly high proportions of chain-initiation and chain-termination products contaminate the chain-propagation products. Use of acetic acid, water, or other hydroxylic (even polar) solvents will favor cleavage of alkoxy radicals. These considerations suggest that additional data on competitive reactions of other tertiary and a few secondary peroxy and alkoxy radicals in oxidations would be useful in supplementing the few data available.

The decreasing protective effect of alkanes on hydroperoxides (RO_2H) at high temperatures is ascribed to formation of dialkyl peroxides (RO_2S) from the solvent (S–H) and reinitiation of chains by the RO_2S. Formation of RO_2S should also occur in oxidations as the temperature increases and the oxygen pressure decreases enough to permit combination of $RO_2\cdot$ with $R\cdot$ radicals. When the hydrocarbon serves as solvent, immediate or delayed initiation by R_2O_2 corresponds to chain propagation by alkoxy radicals to produce alcohols as primary products. Boric acid has been most useful in stabilizing alcohols in oxidations at low oxygen pressures.[17] Its function may therefore be the simple esterification and stabilization of alcohols, possibly unrelated to any special effect of boric acid on hydroperoxides.

Metal-Catalyzed Decompositions

Background.—The literature on metal ion catalyzed decompositions is immense and diverse both in experimental conditions and opinions about the operative

(14) F. D. Greene, M. L. Savitz, H. H. Lau, F. D. Osterholz, and W. N. Smith, *J. Amer. Chem. Soc.*, **83**, 2196 (1961).
(15) J. K. Kochi, *ibid.*, **84**, 1193 (1962).
(16) C. Walling and A. Padwa, *ibid.*, **85**, 1593 (1963).
(17) F. Broick and H. Groseman, *Erdoel Kohle*, **18**, 360 (1965).

mechanisms. Among the reactions which appear to involve free radicals are those (which we call stoichiometric) in which each metal ion decomposes only one or two molecules of hydroperoxide and others (catalytic) in which many hydroperoxide molecules are decomposed.

To determine the mechanisms of catalytic decompositions and the possibilities for controlling their products, we carried out experiments, detailed in part IV[1], on decompositions of *n*-butyl, *sec*-butyl, *t*-butyl, and α-cumyl hydroperoxides in chlorobenzene, mixtures of chlorobenzene with acetic acid or alcohols, and refluxing alkanes, at 0–99°. Cobalt carboxylates were the most frequently used catalysts, but iron phthalocyanine, acetylacetonates of Co^{II}, Co^{III}, Fe^{II}, Fe^{III}, Mn^{II}, V^{III}, and Ce^{IV}, and Nuodex solutions (octoates) of lead, copper, vanadium, and manganese were also tested.

The Role of the Metal Ion.—The products of decomposition of hydroperoxides by catalytic amounts of metal ions are so similar to those from radical-induced reactions over a wide range of solvents and temperatures and so little affected by the choice of metal catalyst, that the mechanistic similarity seems unquestionable. We conclude that the metal ion acts primarily as an initiator *via* one-electron transfer with hydroperoxides. Equation 13 and 14 (where M is

$$\left.\begin{aligned} &M^{n} + RO_2H \longrightarrow \\ &M^{n+1} + RO\cdot + OH^- \end{aligned}\right\} \quad \left.\begin{aligned} &\\ &2RO_2H \longrightarrow RO\cdot + RO_2\cdot + H_2O \end{aligned}\right\} \quad (13)$$

$$\left.\begin{aligned} &M^{n+1} + RO_2H \longrightarrow \\ &M^{n} + RO_2\cdot + H^+ \end{aligned}\right\} \quad (14)$$

metal ion and where OH^- and H^+ may not be formed as free ions, but as part of the metal–ligand complex) provide the cycle whereby one metal ion may destroy much more hydroperoxide.[18]

The radicals formed in eq 13 and 14 initiate the induced chains discussed above. For nontertiary hydroperoxides or for *t*-BuO_2H in protic solvents, the chains may be very short, but the products are the same as in the absence of metal ions. Metal ions may be involved in the chain-terminating steps but radical–radical reactions seem to be the most important route.

Rates of Decomposition.—Rates of decomposition of *n*-BuO_2H, α-cumyl O_2H, and *t*-BuO_2H by cobalt carboxylates in chlorobenzene were proportional to their chain lengths in DBPO-induced decompositions. Rates were first order in $[RO_2H]$ and [Co]; with 10^{-4} *M* cobaltous 2-ethyl hexanoate ($CoOct_2$) at 45°, the half-life of *t*-BuO_2H was 1.3 min. Retardation by millimolar quantities of materials which strongly complex metal ions (carboxylic acids, 1,10-phenanthroline, acetylacetone, or trimethylenetetramine) suggested that complexing of hydroperoxide with the metal ion preceded eq 13 or 14. Small amounts of H_2O or *t*-BuOH did not affect the rate, but, in 2:3 *t*-BuOH–PhCl or 2:3 *i*-PrOH–PhCl, reactions were only $^1/_{500}$th as fast as in chlorobenzene alone, as if the overwhelming concentrations of alcohol were competing with hydroperoxide molecules for bonding sites on the metal ion. In 1:1 AcOH–PhCl, decompositions were very slow. Rates in alkanes were about the same as in chlorobenzene.

Kinetics for reactions in alkanes or mixtures of protic solvents with PhCl were complex as might be expected.

Solubility of Metal Catalysts and Autoretardation.—In addition to the foregoing major reactions of metal-catalyzed decompositions, autoretardation always appeared sooner or later. There was more in alcohol mixtures and alkanes; in refluxing *n*-pentane it occurred so smoothly that the reaction falsely appeared to be third order in hydroperoxide. Clearly the catalyst becomes deactivated as materials are formed which complex and eventually precipitate it. These materials are volatile and are formed in sufficient quantity to instantly deactivate added catalyst. We suspect that formic acid or formaldehyde is the chief offender.

Peroxide decompositions which are first order in metal ion are rare. Depending on solvent, catalyst concentration, and temperature the apparent order ranges from 0.05 to 3. This feature has led other investigators[5,19,20] to propose intricate schemes for metal-catalyzed decompositions. A simple explanation, documented in part IV,[1] is that most metal catalysts are associated to various degrees in organic solvents.

Decompositions by Lead and Magnesium.—We found that lead naphthenate (a Nuodex solution, presumed to be Pb^{II}) catalyzed slow decomposition of *t*-BuO_2H, yielding products indistinguishable from those obtained with more active catalysts. Van Leeuwen and coworkers[21] reported a catalytic effect of Mg^{II} on decompositions of tetralin hydroperoxide at 120°. Their argument that Mg^{II} does not initiate chains is based on the dubious assumption that the hydroperoxide was undergoing thermal homolytic scission at that temperature (part V[1]). Since the participation of Pb^{II} or Mg^{II} in eq 13 and 14 seems most unlikely, we suggest that these results arise from nonradical reactions or, like those of some base-catalyzed decompositions,[7] from trace impurities in the catalysts.

Metal-Catalyzed Autoxidations.—In metal ion catalyzed autoxidations, acetic acid is a good solvent for the metal catalysts and provides a desirable moderator for the metal–hydroperoxide reaction. When the objective is to initiate chains, rather than to decompose hydroperoxide, the rate of radical production in acetic acid leads to longer chains and more efficient use of initiator. On the other hand, a mixture of hydroperoxides and metal catalysts, added to neat styrene, do not give efficient polymerization, nor does it give a long lasting or efficient autoxidation, when added to chlorobenzene solutions of polyisoprene, though the combination is initially effective.[22]

The present work indicates that the chances for effecting chain decompositions of hydroperoxides to *single products* by catalytic amounts of metal ions seem

(18) While other cycles are conceivable, they are inconsistent with the products found with other well-established reaction patterns. Metal ion–free-radical interactions are important in some stoichiometric decompositions (part IV[1]), but catalytic quantities of metals do not usually compete successfully with solvent, hydroperoxide, or other radicals.

(19) H. Berger and A. F. Bickel, *Trans. Faraday Soc.*, **57**, 1325 (1961).

(20) M. H. Dean and G. Skirrow, *ibid.*, **54**, 849 (1958).

(21) H. B. Van Leeuwen, J. P. Wibaut, A. F. Bickel, and E. C. Kooyman, *Rec. Trav. Chim.*, **78**, 667 (1959).

(22) Unpublished work in these laboratories.

small and that there would be little hope for control of products from autoxidation of hydrocarbon by choice of the right metal catalyst. However, vanadium and molybdenum salts catalyze nonradical reactions of hydroperoxides with alkenes to give epoxides,[23] and there are several examples of substantial proportions of boric acid altering the alcohol–ketone ratio in an autoxidation.

Thermal Decompositions

Background.—The difficulty of measuring true rates of thermal homolysis of hydroperoxides is attested by the many attempts which were later found to have failed.[4] Rates were too fast, activation energies too low. Previously we have had some success[24] in reducing the radical-induced decomposition that usually accompanies thermal decomposition by decomposing very dilute solutions of t-BuO_2H in benzene. This approach has been continued in part V.[1]

t-Butyl Hydroperoxide.—Solutions of 0.001 M to 0.26 M t-BuO_2H in toluene were decomposed at 100–215°; similar but less extensive studies were done with benzene, cumene, n-heptane, and cyclohexane. In toluene at 180° the measured first-order rate constant for decomposition at 0.001 to 0.02 M t-BuO_2H was about 2.2×10^{-5}/sec, and had an apparent activation energy of 43 kcal at 170 to 190°. A 40% yield of bibenzyl (based on t-BuO_2H decomposed) showed that at least 40% of the reaction was homolysis, and set a lower limit for k_{15} of 1×10^{-5}/sec. Decompositions

$$t\text{-}BuO_2H \longrightarrow t\text{-}BuO\cdot + \cdot OH \qquad (15)$$

yielded approximately 50% each of acetone and t-butyl alcohol, no O_2, but small amounts of CO and CO_2. Small amounts of acetone were a mild catalyst for the decomposition.

At initial concentrations above 0.02 M, first-order rate constants increased in proportion to $[t\text{-}BuO_2H]_0^{1/2}$ as is common for thermally induced decompositions. Yields of t-butyl alcohol were higher and of bibenzyl, lower. At 100° unexplained factors caused thermal decomposition 20 times as fast as expected from extrapolation of rates at 170–190°.

Decompositions of 0.02 M t-BuO_2H in benzene at 180° had rates similar to those in toluene; in cumene the rates were four times as fast, although a 50% yield of bicumyl showed that homolysis was occurring to the same extent as in toluene (and, therefore, four times as fast). Yields of 28% cumyl alcohol and only 5.8% acetophenone posed an interesting problem, since, if these had cumyloxy radicals as the common precursor, the yields should be in reverse ratio. Seemingly unlikely reactions such as coupling of cumyl and hydroxyl radicals or attack[25] by cumyl radicals on t-BuO_2H have to be reconsidered.

(23) N. Indictor and W. F. Brill, *J. Org. Chem.*, **30**, 2074 (1965); also unpublished work in these laboratories.
(24) R. R. Hiatt and W. M. J. Strachan, *J. Org. Chem.*, **28**, 1893 (1963).
(25) W. A. Pryor, *Tetrahedron Lett.*, 1201 (1963).

$$PhMe_2C\cdot + t\text{-}BuO_2H \longrightarrow t\text{-}BuO\cdot + PhMe_2COH \qquad (16)$$

Decompositions in alkanes at 170–180° appeared to be largely induced, even at the lowest initial concentrations of t-BuO_2H. In both alkylbenzenes and alkanes, RO· and HO· radicals from homolysis of the peroxide readily produced solvent radicals. In alkylbenzene solvents, these radicals were the least reactive and most plentiful radicals and they combined with each other to give bibenzyls. However, in alkanes, the alkyl radicals were too reactive to accumulate. With hydroperoxide they produced alkylperoxy radicals; these scavenged the alkyl radicals to give mixed RO_2S, but at 180° these peroxides decomposed and induced more decomposition.

Decompositions of Other Hydroperoxides.—Some decompositions of n-BuO_2H, sec-BuO_2H, and α-cumyl O_2H in toluene at 170–182° gave rates from two to three times as fast as those found for t-BuO_2H. Yields of bibenzyl showed that these were at least 17–40% homolysis. From other products 21% of n-BuO·, 45% of sec-BuO·, and 60% of α-cumyl-O· radicals are estimated to cleave in toluene at 182° (50% t-BuO· in the previous section).

Implications for Autoxidation.—These results show that below 150° unimolecular homolysis of saturated hydroperoxides does not occur sufficiently rapidly to be a potential source of free radicals. Practically, this limitation is unimportant because faster routes to radical production are usually available (bimolecular decompositions of hydroperoxides[26] and their reactions with carbonyl compounds,[27,28] alkenes,[29–31] surfaces, and trace metals. Theoretically, the limitation is important because of the carelessness with which some workers have discussed unimolecular decompositions without considering the cofactors involved.

Registry No.—n-Butyl hydroperoxide, 4813-50-7; sec-butyl hydroperoxide, 13020-06-9; t-butyl hydroperoxide, 75-91-2; α-cumyl hydroperoxide, 80-15-9.

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Homolytic Decompositions of Hydroperoxides. II.[1a] Radical-Induced Decompositions of *t*-Butyl Hydroperoxide

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Three factors account for deviations from the simplest pattern for the radical-induced decomposition of t-BuO_2H (reactions 1–4 in part I): (1) variation in the ratio of terminating to nonterminating interactions of $2t$-$BuO_2\cdot$ with the viscosity of the medium; (2) competition between the propagation and cleavage reactions of t-$BuO\cdot$ radicals; and (3) competition between hydroperoxide and solvent for t-$BuO\cdot$ radicals. Reactions in the gas phase illustrate all three factors. In solution cleavage is important at high temperatures and low concentrations of *t*-butyl hydroperoxide (as in 0.1 *M* t-BuO_2H in benzene or CCl_4 at 100°) or in hydroxylic solvents (AcOH or t-BuOH) at moderate temperatures. Attack on alkane solvents increases with increasing temperature. Chain lengths of 1 to 50 are observed. Both cleavage and solvent participation result in shorter chains and complex kinetics.

In benzene or chlorobenzene at 25–50°, t-BuO_2H is cleanly decomposed by alkoxy radicals to 90% t-BuOH, 10% t-Bu_2O_2, and 100% O_2. The rate of decomposition is about ten times the rate of initiation and is independent of the concentration of t-BuO_2H.[2] After considering the free-radical-generating efficiencies of the initiators used and the stability of t-BuO_2H in the absence of initiators, this paper deals with induced decompositions in several solvents at 45–100° and in the gas phase at 100°. We show that chain lengths and products vary and that kinetics may be complex, but that the results can be rationalized in terms of a few competing reactions.

Experimental Section

Materials.—t-BuO_2H (90%) obtained from Lucidol Corp. was vacuum distilled to 99+% purity (by iodometric titration). *sec*-Bu_2O_2 and t-$BuO_2C_6H_{11}$ (C_6H_{11} = cyclohexyl) were prepared by the methods of Mosher and coworkers.[3] *sec*-Bu_2O_2 was shown to be pure by iodometric titration and by glpc. The t-$BuO_2C_6H_{11}$ contained about 5% of an unidentified contaminant. t-Bu_2O_2 obtained from the Matheson Co. was shown to be pure by glpc. Di-*t*-butyl peroxyoxalate (DBPO) was prepared by the method of Bartlett and coworkers.[4]

The solvents used were Matheson Chromatograde, refluxed and distilled from CaH_2 before use. Isobutane, *n*-butane, cyclopentane, and cyclopentene were Phillips research grade, used without further purification.

Analytical Procedures. Iodometric Titrations.—t-BuO_2H, *sec*-Bu_2O_2, and DBPO were titrated iodometrically. In the basic technique the sample is added to a mixture of ~20 ml of 90:10 *i*-PrOH–HOAc; about 1 g of NaI is added; and the mixture is refluxed to hasten reaction and exclude air. For hydroperoxides, refluxing the mixture for 2–3 min gave quantitative liberation of I_2. DBPO liberated only 60% of the theoretical amount of I_2, but did so consistently when the amount to be analyzed was kept below 0.05 mmol. Dialkyl peroxides gave no titer under these conditions.

Di-*sec*-alkyl peroxides could be titrated quantitatively if a small amount of metal ion was added. Thus, *sec*-Bu_2O_2 liberated 100 ± 2% of the theoretical iodine when the 20 ml of NaI–HOAc–*i*-PrOH mixture contained 2 μl of a Nuodex solution of iron octoate and reflux time was extended to at least 5 min. Similarly, $FeSO_4$, $FeCl_3$, and Nuodex copper octoate were equally effective catalysts, while use of Nuodex solutions of cobalt or manganese octoate gave no I_2. t-Bu_2O_2 liberated no iodine even with higher concentrations of iron octoate and reflux times up to 20 min. *t*-Butyl cyclohexyl peroxide gave a maximum of 43% of the theoretical amount of iodine under these conditions.

Gas Chromatography.—Most analyses of reacted solutions were made using the Wilkens Model 90 or 350 gas chromatographs with thermal conductivity detectors and 10-ft columns of either 20% Carbowax 20M or 20% diisodecyl phthalate on Chromosorb P. t-Bu_2O_2 was eluted without decomposition, but other peroxides and hydroperoxides were decomposed in the injector cavity or on the column. Solutions containing hydroperoxides were usually reduced to alcohols with triphenylphosphine[5] (Ph_3P) before glpc analysis.

sec-Bu_2O_2 and t-$BuO_2C_6H_{11}$ were analyzed on a Wilkens gas chromatograph with a flame ionization detector ("Hi-Fi") where they were eluted without decomposition from a 5-ft column of 2% diisodecyl phthalate on Chromosorb P. The low-loaded column permitted use of a low temperature (70°), thereby minimizing decomposition. In one instance a solution of t-BuOH, t-Bu_2O_2, and t-$BuO_2C_6H_{11}$ in cyclohexane was analyzed by a combination of fractional distillation, quantitative ir analysis, and glpc.

Procedures for Reactions.—Most reactions in solution were carried out in a series of eight or nine sealed Pyrex ampoules, initially degassed, or with an air atmosphere as indicated in text. Ampoules were immersed in a constant-temperature bath and withdrawn at suitable intervals for iodometric and glpc analysis. Some ampoules were fitted with break-seals and opened on a vacuum line so that the amount of evolved gases could be estimated and samples analyzed by mass spectrometry. For solution reactions carried out under reflux, a cell consisting of a 50-ml bulb sealed to a condenser was immersed in a bath 10–15° warmer than the reflux temperature of the solvent. The solution of hydroperoxide was brought to reflux and reaction was started by addition of the initiator.

Gas phase experiments were carried out in 100-ml Pyrex bulbs with break-seals and capillary inlet tubes. Peroxide and hydroperoxide were added to the evacuated bulbs from a tared syringe. Hydrocarbons were added to some runs by vacuum distillation from a calibrated bulb. Formaldehyde was added in the form of paraformaldehyde. After being heated for appropriate time intervals, the bulbs were connected to the vacuum line and opened, and the contents were distilled into small liquid nitrogen-cooled traps which were then cut out of the line. Less volatile hydrocarbons were distilled with the hydroperoxide. Evolved gases were transferred to a gas buret with a Toepler pump, then analyzed using a Cu–CuO combustion furnace.

Where large amounts of butanes were present, the bulb contents were fractionally distilled under high vacuum at −80°. Blank experiments showed no significant loss of hydroperoxide under these conditions.

Thermal Decompositions of Initiators and of t-BuO_2H

It was necessary to measure rates and efficiences of radical production by some of our initiators before chain lengths of induced decompositions could be evaluated. The possibility of some thermal decompo-

(1) (a) Part I: R. Hiatt, T. Mill, and F. R. Mayo, *J. Org. Chem.*, **33**, 1416 (1968). Equations 1–16 appear in part I. (b) To whom all correspondence should be addressed at Brock University, St. Catherines, Ontario, Canada.

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TABLE I

RATES AND PRODUCTS OF DECOMPOSITIONS OF INITIATORS

Temp, °C	Solvent	$[R_2O_2]_0$, *M*	Decomposition[a] 10^5k_1, sec^{-1}	Decomposition[a] %	Yields on peroxides decomposed, % AcMe	*t*-BuOH	*t*-Bu_2O_2	S—S[b-e]
			t-Bu_2O_2					
100	C_6H_6	0.0066	0.0875	62	96	1.6		
100	C_6H_6	0.245	0.102	70	29	68		20[b]
100	PhMe	0.264	0.0682	22				100[c]
			sec-Bu_2O_2					
100	PhMe	0.10	0.27	83				23[c]
100	PhMe	0.027	0.27	75				25[c]
100	Gas phase	0.0008	0.15[f]	7–82[f]				
			Di-*t*-butyl Peroxyoxalate (DBPO)					
25.0	*t*-BuOH	0.08	1.83	70			10[g]	
37.8	*n*-C_5H_{12}	0.008	10.1	39	0	77	5.4	29[d]
81.5	C_6H_{12}	0.006				92		62[e]

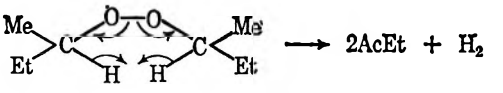
[a] Apparent first-order rate constant and extent of decomposition over which it was measured. [b-e] Products of radical coupling: toluene,[b] bibenzyl,[c] $C_{10}H_{22}$,[d] $(C_6H_{11})_2$.[e] [f] Average of seven runs. [g] See ref 7.

sition of *t*-BuO_2H under the experimental conditions also had to be checked.

Decompositions of Initiators in the Absence of Hydroperoxides. *t*-Bu_2O_2.—At and above 100°, *t*-Bu_2O_2 gave convenient rates of initiation. In toluene at 100°, the first-order rate constant for decomposition of *t*-Bu_2O_2 was found[6] to be 6.8×10^{-7}/sec, and the efficiency of radical production was 100% (measured by the yield of bibenzyl). This rate constant was used for calculation of chain lengths for induced decompositions in both gas phase and solution, although in some of the induced runs the disappearance of *t*-Bu_2O_2, as measured by glpc, was faster (see below). Typical results are shown in Table I.

Di-*t*-Butyl Peroxyoxalate.—DBPO was used to initiate runs at 80° and below. Rate constants for the thermal decompositions of DBPO at several temperatures in benzene and cumene have been given by Bartlett and coworkers.[4] We found the same rates in *n*-pentane and in *t*-BuOH. DBPO has been shown to give about 5% *t*-Bu_2O_2 by a cage reaction in solvents of moderate viscosity (pentane, benzene, HOAc) at 35–45°.[7] In *t*-BuOH and in Nujol, cage recombination accounted for 10 and 76%, respectively, of the radicals formed. For this work we assumed an initiator efficiency of 100% minus the per cent yield of *t*-Bu_2O_2 for the particular solvent.

sec-Bu_2O_2.—Some runs at 100° were initiated by *sec*-Bu_2O_2. Pryor, *et al.*,[8] have shown that this peroxide initiates the polymerization of styrene at 80° about as rapidly as *t*-Bu_2O_2 does. We have measured rates of decomposition at 100° in toluene and in the gas phase (Table I) using both glpc and a modified iodometric titration for peroxide analysis. Rates were first order in peroxide, and about four times as fast in solution as for the decomposition of *t*-Bu_2O_2, but the efficiency of radical production in solution, as measured by the yield of bibenzyl, was only 25%. Analysis of the other products of decomposition (Table I) gave an unexpected 25–30% hydrogen gas, which might be explained by a concerted decomposition of the kind discovered by Mosher and Durham[9] for primary hydroperoxy hemiacetals.



The gas phase decomposition of *sec*-Bu_2O_2 was first order, but only 2.7 times as fast as decomposition of *t*-Bu_2O_2: $k_d = 1.8 \times 10^{-6}$/sec. The faster rate in solution suggests more chain decomposition due to the higher concentrations used.

Decomposition of *t*-BuO_2H in the Absence of Initiators.—Thermal decompositions of *t*-BuO_2H in solution are treated extensively in part V. At 100° or below, 0.1 *M* *t*-BuO_2H decomposed less than 1% in 2 days, a negligible contribution to the induced decompositions which usually lasted no longer than 15 hr.

Early experiments showed low but erratic rates of decomposition, 4–12% in 15 hr, in the gas phase at 100°. In subsequent work with a second batch of purified hydroperoxide, rates were considerably higher, 6–27% in 15 hr. Using new vessels or vessels which had been treated with NaOH[10] narrowed the range to 4.4–10.2%. (An average rate of decomposition for 0.007 *M* *t*-BuO_2H was $3.6–7.9 \times 10^{-7}$ mole/l. min.$^{-1}$). Addition of cyclopentene (which should have quenched any radical chain decomposition) had no effect. This higher rate is apparently connected with surfaces and with otherwise indistinguishable differences between batches of hydroperoxide. It was not caused by the presence of *t*-Bu_2O_2 as an impurity; as will be shown, about 10% *t*-Bu_2O_2 would be required to give the average rates above.

Induced Decompositions of *t*-BuO_2H in Solution

Decompositions at >0.2 *M* in Benzene at 100°.—At concentrations of *t*-BuO_2H above 0.2 *M* *t*-Bu_2O_2-induced decompositions gave *t*-BuOH, O_2, and, presumably, *t*-Bu_2O_2;[11] yields of acetone were negligible. The rate of decomposition was independent of [*t*-BuO_2H] to at least 50% decomposition. The rather

(6) This value is close to the value (5.0 ± 2.5) × 10^{-7}/sec obtained by extrapolation from the 130–150° gas phase data of L. Batt and S. W. Benson [*J. Chem. Phys.*, **36**, 895 (1962)].

(7) R. Hiatt and T. G. Traylor, *J. Amer. Chem. Soc.*, **87**, 3766 (1965).

(8) W. A. Pryor, D. M. Huston, T. R. Fiske, T. L. Pickering, and E. Ciuffarin, *ibid.*, **86**, 4237 (1964).

(9) H. S. Mosher and L. J. Durham, *ibid.*, **82**, 4537 (1960), and preceding papers.

(10) Heated with 10% NaOH for 30 min at 100°, rinsed repeatedly with water, and oven dried.

(11) The concentration of the initiator, within the accuracy of the glpc analyses, remained constant, as if all terminations gave *t*-Bu_2O_2.

wide variation in chain length, 23–32 in Table II, was probably due to some "thermal" decomposition at these high concentrations of hydroperoxide.

TABLE II

t-Bu_2O_2-INDUCED DECOMPOSITIONS OF *t*-BuO_2H IN BENZENE AT 100°

$[t\text{-}Bu_2O_2]_0$, *M*	$[t\text{-}BuO_2H]_0$, *M*	Chain length[a]	Yields on *t*-BuO_2H decomposed, % AcMe	*t*-BuOH	O_2
0.246	0.878	30.0			
0.251	0.554	32.0			100
0.247 (*sec*-Bu_2O_2)	0.199	23.3	4	82	
0.248	0.506	12[b]			

[a] Moles of *t*-BuO_2H destroyed/mole of initiating radicals. [b] Average for first 2 hr, corrected to 25% efficiency of *sec*-Bu_2O_2.

The principal difference between these results and those previously reported[2] for decompositions initiated by DBPO in benzene or chlorobenzene at 25 to 45° is the longer chain length, paralleled by the lower viscosity of benzene at 100°:

$$\frac{\text{specific viscosity at } 35°}{\text{specific viscosity at } 100°} = 2.5$$

$$\frac{\text{chain length at } 100°}{\text{chain length at } 35°} = 2.7$$

The factor 2.7 corresponds to an activation energy for escape of alkoxy radical pairs from the cage to continue the chain (eq 3[1a]) which is 3.5 kcal/mol higher than for their cage reaction with each other to give *t*-Bu_2O_2 (eq 4[1a]).

A more striking example of viscosity control is thermal decomposition at 35° of 0.03 *M* DBPO in Nujol containing 0.1 *M* *t*-BuO_2H. The result, *no* hydroperoxide decomposed, is due partly to competition by the Nujol for alkoxy radicals but mostly to a viscosity effect. (DBPO itself is no more than 24% efficient in producing free radicals in this very viscous medium,[7] and we infer that few, if any, alkoxy radical pairs, if produced by interactions of 2*t*-$BuO_2\cdot$, would escape from the solvent cage.)

sec-Bu_2O_2 was used to initiate one decomposition in benzene at 100° (Table II). Products were not analyzed, but the results prove that some pairs of *sec*-$BuO\cdot$ radicals are able to escape from the solvent cage. The indicated initial chain length, 12, depends too much on the uncertain efficiency of the initiator (*vide supra*) to permit comparison with runs initiated with *t*-Bu_2O_2.

Decompositions with Cleavage of *t*-$BuO\cdot$ Radicals.—Decompositions of 0.1 *M* *t*-BuO_2H at low concentrations (0.1 *M*) in solvents without reactive hydrogen gave up to 30% yields of acetone as cleavage products. Reaction chains were short and the kinetics complex. These results and their implications are discussed below.

Low Concentrations of *t*-BuO_2H in Benzene at 100°.—The results of *t*-Bu_2O_2-initiated decompositions of 0.02–0.1 *M* *t*-BuO_2H in benzene are shown in Table III. Runs were generally carried to 50–100% decomposition of *t*-BuO_2H and 2.5–5% decomposition of *t*-Bu_2O_2. The products included acetone (but no methanol), *t*-BuOH, CO, CO_2, and a small amount of O_2. Relative yields of acetone and *t*-BuOH were dependent on the

TABLE III

INDUCED DECOMPOSITIONS OF *t*-BUTYL HYDROPEROXIDE WITH HIGH CLEAVAGE OF *t*-BUTOXY RADICALS[a]

$[I]_0$,[a] *M*	k_d[b] × 10^7, sec^{-1}	$[t\text{-}BuO_2H]_0$, *M*	Chain length[c]	Yields on *t*-BuO_2H decomposed, % AcMe	*t*-BuOH	*t*-Bu_2O_2
In Benzene at 100°, Initiation by *t*-Bu_2O_2						
0.246[d]		0.096	15.9			
0.245[d]	7.16	0.091	13.3	20	79	
0.241[d]	6.86	0.081		27	75	
0.245		0.021	5.14			
0.0510[d]		0.098	20.1			
0.0196[d]		0.100	15.8			
0.0103[d]		0.120	7.0			
0.247[e]	11.2	0.093	12.8			
0.247[e]		0.026	4.7			
0.048[e]		0.094	9.3			
0.0071[e]		0.0083	0			
In CCl_4 at 100°, Initiation by *t*-Bu_2O_2						
0.210[e]		0.0868	11.2			
0.0498[e]		0.0818	11.6			
0.0425[e]	21.7	0.0733	11.2	12		
0.0466[e]	19.2	0.0182	4.1	13		
0.0133[e]		0.0389	9.7			
In Acetic Acid at 45°, Initiation by DBPO						
0.0164[e]		0.137	1.57[f]	25	68	7
In *t*-BuOH at 45°, Initiation by DBPO						
0.0232[e]		0.202	1.11[f]	17		14
0.0409[e]		0.117	0.54[f]			

[a] Initial concentration of initiator. [b] Apparent average rate constant for disappearance of initiator. [c] Initial chain length calculated using $R_i = 2 \times 6.86 \times 10^{-7}$ $[t\text{-}Bu_2O_2]_0$ from third experiment unless otherwise indicated. [d] In sealed tubes in absence of air. [e] In sealed tubes in presence of air. [f] Average chain length for complete decomposition of initiator.

concentration of *t*-BuO_2H, since *t*-$BuO\cdot$ could either cleave or abstract hydrogen from the hydroperoxide. Some *t*-BuOH appears to be formed by reaction of *t*-$BuO\cdot$ radicals with a radical–benzene adduct, but this reaction becomes important only at very low concentrations of *t*-BuO_2H.

For individual runs, plots of long $[t\text{-}BuO_2H]$ *vs.* time were linear to at least 80% decomposition. For the several runs, eq 17[1a] applies. Chain lengths thus

$$-d[t\text{-}BuO_2H]/dt = k[t\text{-}Bu_2O_2]^{\sim 1}[t\text{-}BuO_2H]^{\sim 1} \quad (17)$$

were proportional to $[t\text{-}BuO_2H]$ and those in Table III were calculated from initial rates determined graphically. The concentration of *t*-Bu_2O_2, determined by glpc, also decreased (Table III), showing that interaction of *t*-butylperoxy radicals was not the sole termination reaction.[12]

To see how much termination, if any, resulted in formation of *t*-Bu_2O_2, some decompositions at 100° in benzene were initiated by ABN (Table IV). The fast decomposition of ABN at 100° (half-life about 7 min)[13] precluded rate measurements but products were determined. Ampoules were heated for 100 min and analyzed by titration for residual *t*-BuO_2H and by glpc after the hydroperoxide had been reduced with Ph_3P. Over-all chain lengths and yields of acetone varied with $[t\text{-}BuO_2H]$, as in runs initiated by *t*-

(12) This decrease was only a few per cent of the total concentration of *t*-Bu_2O_2 and had negligible effect on the rate of initiation during a run, but it was significantly different from runs at high concentrations of *t*-BuO_2H where $[t\text{-}Bu_2O_2]$ remained constant within the accuracy of the analysis.

(13) J. P. Van Hook and A. V. Tobolsky, *J. Amer. Chem. Soc.*, **80**, 780 (1958).

TABLE IV

DECOMPOSITIONS OF t-BuO_2H BY ABN IN BENZENE[a] AT 100°

[ABN]$_0$	$10^5[R_i]_0$, mol/l. sec^{-1}	[t-BuO_2H]$_0$, M	$-\Delta[t\text{-}BuO_2H]$ / 1.2[ABN]$_0$	Yields on t-BuO_2H decomposed, %[b] [Acetone]$_t$	[t-Bu_2O_2]$_t$
0.00828	3.0	0.263	14.1	7.1	5.0
0.00828	3.0	0.132	8.5	12	4.4
0.00166	0.6	0.134	14.4	18	4.4

[a] In O_2-saturated sealed tubes for 100 min, 14 half-lives for ABN. [b] Remainder of t-BuO· was in t-BuOH. Analyses of these three products accounted for 99% of original t-BuO_2H in each run.

Bu_2O_2, but in each run the yield of t-Bu_2O_2 accounted for 4.4–5% of the t-BuO· groups from decomposed hydroperoxide. This number provides another measure of the ratio of nonterminating to terminating interactions of 2t-BuO_2· radicals (k_3/k_4) in benzene at 100°, since all hydroperoxide decomposes through t-BuO_2·radicals; 100/4.4 = 22, in fair agreement with the chain lengths (23 to 32) found at high concentrations of t-BuO_2H.

Some unexpected effects of oxygen were found in reactions initiated by ABN and t-Bu_2O_2. A solution of 0.1 M t-BuO_2H and 0.01 M ABN in benzene, refluxed to remove any O_2 that might be formed during decomposition, underwent no change in peroxide titer over many hours. For the decompositions in Table IV, ampoules were sealed in an atmosphere of O_2. Apparently the Me_2CCN radical does not attack hydroperoxides efficiently, but the corresponding peroxy or alkoxy radical does.

On the other hand, oxygen retarded the t-Bu_2O_2-initiated runs in benzene, the effect being most pronounced at the lowest initial concentrations of t-BuO_2H (Table III). Initially degassed runs with 0.02 M [t-BuO_2H]$_0$ showed marked autoretardation as the reaction proceeded, and O_2 was produced by the decomposition. This effect was not found in any other solvent, or in the gas phase, and may be due to formation of phenols. We found that ampoules of 0.27 M t-Bu_2O_2 in benzene sealed in an air atmosphere and heated for 15–20 hr at 100° developed a small hydroperoxide titer. Apparently some of the methylperoxy radicals which are formed abstract H· from benzene (or from t-$BuOC_6H_6$·) to form MeO_2H. Production of small quantities of methyl hydroperoxide would lead to artificially high titers for [t-BuO_2H] in runs of low [t-BuO_2H]$_0$. The MeO_2H might retard the induced decomposition as well.

In CCl_4 at 100°.—Because the complex results reported above seemed related to the formation of methyl radicals, and because Walling and Wagner[14] reported less cleavage of t-BuO· radicals in CCl_4 than in benzene, we carried out some t-Bu_2O_2-initiated decompositions of t-BuO_2H in CCl_4. With 0.08 M t-BuO_2H, the yield of acetone was about half that in benzene (Table III) (confirming Walling and Wagner's results), and so our work was not carried very far. Chain lengths and kinetics for decomposition were similar to those found in benzene.

In Acetic Acid and in t-BuOH at 25–45°.—In addition to a reported retardation of DBPO-induced decomposition by t-BuOH,[15] we observed (part IV) similar retardations of the (Co^{II})-catalyzed decomposition of t-BuO_2H in alcohols and in acetic acid at 25–45°. The decompositions in t-BuOH and in AcOH, summarized in Table I, were carried out to check these results and determine the products. Decomposition of DBPO, a convenient initiator at these temperatures, was carried to completion and only products and over-all chain lengths of decomposition were determined. In both solvents yields of acetone were comparable with those in benzene at 100° but chain lengths were shorter, 1.5 or less.

Discussion.—All the reactions discussed in the preceding section have large yields of acetone, low yields of oxygen where measured, and complex rate expressions. All of these features are associated with the generation of methyl radicals, their scavenging of oxygen, and their participation in termination reactions such as[16] those in eq 18 and 19 which are apparently

$$Me\cdot + t\text{-}BuO_2\cdot \longrightarrow MeO_2\,t\text{-}Bu \qquad (18)$$

$$Me\cdot \xrightarrow{O_2} MeO_2\cdot \xrightarrow{t\text{-}BuO_2\cdot} CH_2O + t\text{-}BuOH + O_2 \qquad (19)$$

much faster than attack by Me· on t-BuO_2H. To the extent that each Me· radical produced takes part in one of these termination reactions, the cleavage of t-BuO· to Me· radicals becomes rate-controlling for termination and, as pointed out in part I[1a] (eq 8),

$$-d[t\text{-}BuO_2H]/dt = R_i k_2[t\text{-}BuO_2H]/2k_7 \qquad (8)$$

close to that determined experimentally in benzene and in CCl_4.[17]

That basic features of the induced decomposition mechanism[18] are retained even in these more complex situations is shown by the results with ABN in benzene at 100°. Here the kinetics are complex, but the yield of t-Bu_2O_2 is nearly constant, independent of chain length and initiator efficiency. The ratio of nonterminating to terminating interactions of $2RO_2$·, k_3/k_4, though no longer the same as the chain length (to which other terminations contribute), can be measured by the yield of t-Bu_2O_2.

The low chain lengths in t-BuOH may be due partly to its high viscosity relative to benzene or acetic acid, which would increase the proportion of terminating to nonterminating interactions of 2t-BuO_2· radicals. However, we have a measure of this effect in the relative proportions of t-BuO· radicals which escape when produced by thermal decomposition of DBPO (95% in benzene or acetic acid, 90% in t-BuOH at 45°[7]) and it is slight.

(14) C. Walling and P. J. Wagner, *J. Amer. Chem. Soc.*, **86**, 3368 (1964).
(15) T. G. Traylor, personal communication, 1965.
(16) F. H. Seubold, F. F. Rust, and W. E. Vaughan, *J. Amer. Chem. Soc.*, **73**, 18 (1951).
(17) Since reaction orders in initiator and hydroperoxide were always slightly less than one, eq 7 is probably the major, but not the only, termination. When eq 4 controls termination, the order in [t-BuO_2H] approaches zero (eq 5). When Me· radicals do not terminate but abstract hydrogen from t-BuO_2H, then reaction order approaches $^1/_2$ in R_i. A complete solution of the steady-state equation is too complex to be useful.
(18) S. W. Benson, *J. Chem. Phys.*, **40**, 1007 (1964).

TABLE V

INDUCED DECOMPOSITIONS OF t-BuO_2H IN REFLUXING ALKANES

Temp, °C	Solvent	[DBPO]$_0$, M	[t-BuO_2H]$_0$, M	Chain length[a]	S—OH, %[b,c]	S=O, %[b,d]
98.6	n-Heptane[e]	0.254	0.0797	~1[f]		
81.5	Cyclohexane	0.0169	0.104	0.97	70 (55[f])	17 (32[f])
81.5	Cyclohexane	0.061	0.098	0.84		
81.5	Cyclohexane	0.0120	0.091	0.83	99	11
81.5	Cyclohexane	0.0081	0.0419	0.47		
81.5	Cyclohexane	0.0205	0.0285	0.38	69 (69[f])	29 (29[f])
37.8	n-Pentane	0.0112	0.196	5.9[g]		
37.8	n-Pentane	0.0076	0.118	2.9[h]	Present	40

[a] [t-BuO_2H decomposed]/2[DBPO]. Reactions were carried out to complete decomposition of DBPO, 30 hr at 37.8°, 0.5 hr at 81.5°. [b] Products by glpc in % of t-BuO_2H decomposed; many are secondary products (see text). [c] Alcohol derived from solvent. [d] Ketone derived from solvent. [e] Initiated by t-Bu_2O_2. [f] By glpc before reduction of product mixture with Ph_3P. [g] Initial chain length; average chain length for complete decomposition of DBPO = 2.9. [h] Initial *and* average chain length: 2.7% AcMe, 89% t-BuOH, and 8.5% t-Bu_2O_2.[t]

Walling and Wagner[14] have observed that solvents influence the propensity of t-BuO· to cleave rather than abstract hydrogen from a substrate. We find also that, at least in benzene, cleavage is more temperature-dependent than abstraction. More novel is the large effect of a few methyl radicals on the induced decomposition of t-BuO_2H.

Solvents with Reactive Hydrogen. Refluxing Alkanes.—In gas phase oxidations at 100°, induced decomposition of t-BuO_2H is retarded by some hydrocarbons. We suspected that alkyl radicals, resulting from hydrogen abstraction by t-BuO·, might act like methyl radicals resulting from cleavage of t-BuO· radicals. We have tested this hypothesis by investigating decomposition products of t-BuO_2H in alkane solvents at several temperatures. These solvents were refluxed in an effort to expel oxygen and prevent autoxidation during the reaction.

t-BuO_2H (0.1 M) was stable almost indefinitely in the presence of 0.28 M t-Bu_2O_2 in refluxing n-heptane (98.6°), although chain lengths in benzene at 100° (Table I) were about 15. In DBPO-initiated decompositions in cyclohexane (81.5°) and in n-pentane (37.8°), protection by the solvent was less complete. Chain lengths in Table V are based on initial and final hydroperoxide titers after complete decomposition of DBPO.[19] The formation of alkyl hydroperoxides in some runs (see below) complicates the interpretation of these numbers, but it is clear that chains are longer at lower temperatures and higher initial concentrations of t-BuO_2H.

The products included t-BuOH and significant yields of t-BuO_2S (where SH is solvent). Yields of acetone were small; O_2 was not measured. *No* solvent dimers were produced, though these were found when DBPO was decomposed in the absence of t-BuO_2H (Table I).

Products determined by glpc analysis are shown in Table VI. Most of the alcohols and ketones shown are not the primary products but the pyrolysis products, during gas chromatography, of solvent peroxides,[20] t-BuO_2S and SO_2H (S is solvent). For example, combination of quantitative ir with glpc data showed that the true products of the last run with cyclohexane were 75% t-BuO_2H_{11}, 10% t-Bu_2O_2, and 11% cyclohexene; yields are on DBPO decomposed to show that 96% of radical termination products are accounted for. Refinement of our glpc techniques gave for the second cyclohexane run, carried to 100% decomposition of hydroperoxide *via* successive additions of DBPO, 60% t-$BuO_2C_6H_{11}$, 13% cyclohexanol, and 6.5% cyclohexanone.

Some solvent hydroperoxide was also formed. This claim rests on finding *some* cyclohexanone and cyclohexanol when reaction was carried to completion, and, in runs not carried to completion, on a shift in cyclohexanone–cyclohexanol ratio depending on whether the solutions had, or had not, been reduced with Ph_3P prior to glpc analysis under pyrolytic conditions.

$$C_6H_{11}O_2H \xrightarrow[\Delta]{\text{glpc}} C_6H_{10}O + C_6H_{11}OH$$

$$C_6H_{11}O_2H \xrightarrow{Ph_3P} C_6H_{11} \xrightarrow{\text{glpc}} C_6H_{11}OH$$

n-Heptane at 170°.—Although n-heptane completely protected 0.1 M t-BuO_2H from induced decomposition at 100° (Table V), it did not prevent decomposition at 170°. Figure 1 shows that added t-Bu_2O_2 enhanced the rate of disappearance of titratable hydroperoxide over that for the normal thermal decomposition and that this action persisted long after the initial t-Bu_2O_2 should have been completely decomposed (half-life[6] about 8 min at 170°). A chain length of 6 was calculated by comparison of initial thermal and induced rates. In benzene at 170°, the thermal decomposition of t-BuO_2H had been only slightly affected by added t-Bu_2O_2 (part V). The products from the heptane runs were not analyzed.

Discussion.—Although a thorough understanding of induced decompositions of hydroperoxides in alkanes would require more product studies (including a method for distinguishing between different kinds of hydroperoxides in reacted solutions), the results above permit us to define the important features. Most interesting is the maximum stabilizing effect of alkanes near 100°. This effect probably results from the preferential re-

(19) For two of the runs in n-pentane, the reaction mixture was sampled at several points and residual RO_2H was determined by titration and by subtracting a calculated titer for undecomposed DBPO. In one of these the chain length was constant throughout the reaction. In the other, the initial chain length was higher than this but decreased drastically as the run proceeded, so that the over-all chain length was the same. We do not understand these results.

(20) These did not arise from air. Decomposition of DBPO in refluxing alkanes in the absence of t-BuO_2H gave only olefins and solvent dimers (Table I). In only one case was more oxygen found in solvent products than would have come from decomposed t-BuO_2H; here the DBPO was introduced into the refluxing solution of t-BuO_2H and cyclohexane in 1 ml of air-saturated solvent. In all other runs it was added as a solid to the refluxing mixture.

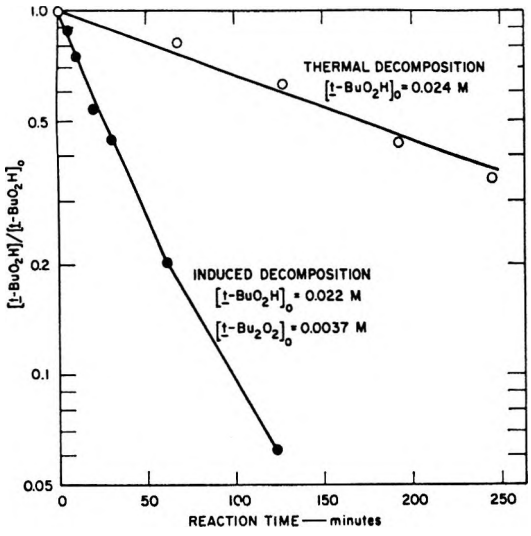


Figure 1.—Decompositions of 0.02 M t-BuO_2H in n-heptane at 170°

action of RO· radicals with solvent instead of with hydroperoxide, and is of course dependent on $[RO_2H]$.

At lower temperatures, more RO· radicals attack hydroperoxide because of the higher activation energy for solvent attack.[21] Much above 100°, termination products such as RO_2S and olefin accelerate decomposition of hydroperoxide, offsetting the retarding effect of the solvent. The situation is further confused by the formation of alkyl hydroperoxides, probably from solvent radicals and oxygen formed from interaction of 2t-BuO_2· radicals (eq 20 and 9) followed by chain

$$S\cdot + O_2 \longrightarrow SO_2\cdot \quad (20)$$

$$RO\cdot + SH \longrightarrow ROH + S\cdot \quad (9)$$

termination (eq 21 or 10). The high yields of SO_2R

$$S\cdot + RO\cdot \longrightarrow ROH + \text{olefin} \quad (21)$$

$$S\cdot + RO_2 \longrightarrow SO_2R \text{ (or } RO_2H + \text{olefin)} \quad (10)$$

show that t-BuO_2· radicals are the predominating radicals in these systems and effectively scavenge S· radicals. This conclusion agrees with our own unpublished esr results and those of Thomas.[22]

Gas Phase Decompositions of t-BuO_2H by Free-Radical Initiators

Decompositions Initiated by t-Bu_2O_2 at 100° Rates.—In a typical gas phase mixture of 0.004 M t-BuO_2H and 0.001 M t-Bu_2O_2, t-BuO_2H decomposes to the extent of 25–30% in 15 hr at 100°. Table VI summarizes the effects of initial concentrations of t-Bu_2O_2 on rates of decomposition of t-BuO_2H. In these runs conversions of t-BuO_2H varied from 11 to 62% and of t-Bu_2O_2, from 2 to 4%.

Although both the radical-induced and thermal decompositions contribute to the measured rates of disappearance of t-BuO_2H, no corrections for the thermal rate have been applied here because of the erratic nature of these reactions and our lack of a firm basis for such corrections. For most experiments in Table VI we used a single sample of t-BuO_2H which gave thermal rates that are generally about 10% of the induced rates in experiments having comparable amounts of hydroperoxide.

(21) Shorter chain lengths in cyclohexane than in pentane may result partly from much more rapid initiation by DBPO at 81.5° than at 37.8°. However, the very short chains with slow initiation by t-Bu_2O_2 in n-heptane at 98.6° show that the rate of initiation is less important than temperature in controlling chain lengths.

(22) J. R. Thomas, *J. Amer. Chem. Soc.*, **87**, 3935 (1965).

TABLE VI

EFFECTS OF t- AND sec-Bu_2O_2 ON RATES OF GAS PHASE DECOMPOSITIONS (R_{HP}) OF t-BUTYL HYDROPEROXIDE AT 100°[a]

Run no.	Time, min	$[Bu_2O_2]_0$, initial	$[t\text{-}BuO_2H]_0$, mM	% conversion of t-BuO_2H	R_i,[a] mol/l. min × 10^7	R_{HP}, mol/l. min × 10^7	Chain length, R_{HP}/R_i
			t-Bu_2O_2				
69A	495	0.918	0.622	37	0.75	4.6	6.1
69B	495	0.952	0.663	41	0.78	5.5	7.0
65A	900	0.862	0.79	51	0.70	4.0	5.7
65B	900	0.925	1.58	62	0.75	6.6	8.8
65C	900	0.926	2.58	35	0.76	10.0	13
69C	495	0.986	3.17	18	0.80	12.0	15
67A	1120	0.466	4.25	22	0.380	8.4	26
67B	1120	1.10	4.39	33	0.90	13	15
67C	1120	1.74	4.31	43	1.4	16	12
67D	1120	3.11	4.53	52	2.5	21	8.4
67E	1120	4.36	4.20	67	3.6	25	6.7
65D	900	0.938	4.82	24	0.77	13.0	17
69D	495	0.964	8.84	11	0.79	19.0	24
65E	900	0.921	11.0	21	0.75	25.0	33
69F	495	0.958	14.86	13	0.78	38.0	49
			sec-Bu_2O_2				
86M	929	0.960	8.91	39	2.1	37.0	18
86O	944	0.927	8.99	29	2.0	28.0	14

[a] Calcd from data in Table I: $R_i = 2k_d[Bu_2O_2]_0$, where $k_d = 6.8 \times 10^{-7}$ sec^{-1}($t^{1/2}$ = 283 hr) for t-Bu_2O_2 and $k_d = 18 \times 10^{-7}$ sec^{-1}($t^{1/2}$ = 107 hr) for sec-Bu_2O_2.

A log–log plot of the rate of hydroperoxide decomposition *vs.* $[t\text{-}Bu_2O_2]_0$ (runs 67A–E, Table VI) gave a good straight line with a slope of 0.5. The plot of change in rate with average concentration of t-BuO_2H (runs 69A–F and 65B–E) showed marked deviation from linearity (too fast) at the highest concentrations. These data could be fitted about equally well to lines with slopes of 0.5 and 1. Thus the over-all rate law for the induced decomposition takes the form of eq 11

$$R_{HP} = k(R_i)^{1/2}[\text{ROOH}]^{1/2-1} \quad (11)$$

and

$$\text{chain length} = R_{HP}/R_i = k[t\text{-}BuO_2H]^{1/2-1}/2k_d[t\text{-}Bu_2O_2]^{1/2} \quad (22)$$

At the highest concentration of hydroperoxide used (almost 0.015 M in 69F), each t-BuO· radical decomposes 40–45 hydroperoxide molecules, wall catalysis accounting for the other 5–10.

Products.—Because so little material was available from each run, analyses for products and for remaining hydroperoxide were done on duplicate runs. In a typical experiment, 1.26 mmol of t-BuO_2H was 55.6% decomposed in 950 min (by t-Bu_2O_2 initially 0.888 mM), giving 84.6% t-BuOH, 4.5% acetone, and 32% O_2. In general, yields of acetone were 5–10%. More than 90% of the t-butoxy radicals formed was accounted for in analyses as AcMe or t-BuOH, but only a third to a half of the theoretical amount of oxygen was liberated. The remainder might be accounted for by reaction with methyl radicals to give CO_2.

The yield of t-Bu_2O_2 (the only termination product when t-BuO_2H is decomposed by DBPO at 45°)[2]

was estimated using *sec*-Bu_2O_2 as the initiator. In a close duplicate of run 69D (Table VI), 0.93 m*M* *sec*-Bu_2O_2 and 8.86 m*M* *t*-BuO_2H were heated for several half-lives of the initiator. All the *t*-BuO_2H decomposed with an estimated average chain length of 10. Although 0.45 m*M* yield of *t*-Bu_2O_2 is expected from the amount of chain initiation (see below), glpc analysis showed only 0.05 m*M* *t*-Bu_2O_2 to be formed.[23] Thus for these short chains, few terminations result from interactions of 2*t*-$BuO_2\cdot$ radicals. The significant yield of acetone (and methyl radicals) suggests an alternate route. A low termination tendency of 2*t*-$BuO_2\cdot$ in the gas phase is consistent with the long chains found at high [*t*-BuO_2H] (Table VI).

Initiation Efficiency of *sec*-Bu_2O_2 in the Gas Phase.—The first experiments with *sec*-Bu_2O_2 and *t*-BuO_2H were done to establish that *sec*-$BuO\cdot$ could be generated satisfactorily in the gas phase and that it would initiate a chain with *t*-BuO_2H. The two runs (runs 86M and O in Table VI) gave rates of disappearance of hydroperoxide somewhat faster than comparable experiments using *t*-Bu_2O_2. With 65E as comparison (and correcting for a first-power dependence on hydroperoxide concentrations) we found that *t*-BuO_2H disappears 1.5 times as fast in 86M and 1.8 times as fast in 86O. In the gas phase, *sec*-Bu_2O_2 decomposes about 2.7 times as fast as *t*-Bu_2O_2 (Table I). If the two peroxides are equally efficient in radical production and self-destruction, we would expect $(2.7)^{1/2}$ or 1.6-fold greater rate for the reaction with secondary peroxide. This factor of 1.6 (perhaps only by coincidence) is remarkably close to the experimental value, and strongly suggests that the low efficiency of *sec*-Bu_2O_2 in toluene was due to disproportionation of pairs of *sec*-$BuO\cdot$s in solvent cage and/or induced decomposition of the peroxide.

Retardation by Added Hydrocarbons.—Addition of hydrocarbons to the gas phase decompositions decreased the chain lengths of induced decompositions in proportion to the concentration of added material and its reactivity[24] toward alkoxy radicals. The chain length for 2.0 m*M* *t*-BuO_2H with 1.0 m*M* *t*-Bu_2O_2 (about 15 with no additive, Table VI) was about 1.0 when 29 m*M* cyclopentene was added. The same effect was achieved with about 250 m*M* or 270 m*M* isobutane.

Whereas results are in accord with reactions in solution, they are particularly interesting because they suggest that removal of a hydrogen atom from hydroperoxide (O_2H) by an alkoxy radical is very much faster than from hydrocarbons having hydrogens with bond strengths equal to or lower than that of *t*-butyl hydroperoxide [$H°_D(O_2\text{–H})$ = 90 kcal], cyclopentane or isobutane [$H°_D(\text{C–H}) \simeq 91$], and cyclopentene [allylic $H°_D(\text{C–H}) \sim 78$].[25] In these reactions, activation energies for abstraction are not a constant fraction of bond strength, being a much smaller fraction for RO_2–H than for C–H. Thus even at low concentrations (1%) in the gas phase, hydroperoxide can compete effectively for alkoxy radicals.

(23) While during the time of reaction (about one half-life for *t*-Bu_2O_2) any *t*-Bu_2O_2 formed will also have partially decomposed, clearly the amount remaining will be *at least* half of the total produced.

(24) P. Gray and A. Williams, *Chem. Rev.*, **59**, 270 (1959).

(25) S. W. Benson, *J. Chem. Educ.*, **42**, 5021 (1965).

Comparison of Gas and Liquid Phase Decompositions

Our measurement of rates, chain lengths, and products of decompositions of hydroperoxides and the effects of alkanes on these show that the basic features of the gas phase and liquid phase reactions are the same. Both reactions involve the two pairs of competing reactions, terminating and nonterminating reactions of peroxy radicals (eq 3 and 4) and propagation

$$2t\text{-}RO_2\cdot \rightarrow 2RO\cdot + O_2 \quad (3)$$

$$2t\text{-}RO_2\cdot \rightarrow R_2O_2 + O_2 \quad (4)$$

and cleavage of *t*-alkoxy radicals (eq 9 or 2 and 7).

$$RR'R''CO\cdot + SH \text{ (or } RO_2H) \longrightarrow RR'R''COH + S\cdot \text{ (or } RO_2\cdot) \quad (9 \text{ or } 2)$$

$$RR'R''CO\cdot \longrightarrow R'COR'' + R\cdot \quad (7)$$

Interactions of *t*-$BuO_2\cdot$ radicals in the liquid phase produce more free *t*-$BuO\cdot$ radicals and less termination as the temperature increases. This effect may be due either to the decreasing viscosity of the solvent or to the higher activation energy[22] for eq 3 over eq 4 or to both. In the gas phase where there is no solvent cage, termination by 2*t*-$BuO_2\cdot$ radicals becomes negligible: the same kinetic order for termination as for generation of *t*-$BuO\cdot$ radicals must lead to rates dependent on the first power of initiator, but the rate is clearly dependent on [initiator]$^{1/2}$.

If termination is by two free *t*-$BuO\cdot$ radicals as in

$$2t\text{-}BuO\cdot \longrightarrow t\text{-}Bu_2O_2 \quad (23)$$

then eq 24 can be written as shown. This mechanism

$$-d[t\text{-}BuO_2H]/dt = k_2[t\text{-}BuO_2H](R_i/2k_{24})^{1/2} \quad (24)$$

may apply at high concentrations of *t*-BuO_2H where cleavage of *t*-$BuO\cdot$ is suppressed, but it does not apply when chains are short. Using data from run 69F (Table VI) to solve eq 24 for k_2 gives ~400 l./mol sec, a reasonable value.[26]

The second set of competing reactions is given in eq 9, 7, and 2 of alkoxy radicals. The reaction in eq 2 tends to continue the decomposition chain but eq 9 and 7 tend to terminate the chains at or below 100° because they produce alkyl radicals. Whereas these alkyl radicals are capable of abstracting hydroperoxide hydrogen to continue decomposition chains, the relatively large steady-state concentration of *t*-$BuO_2\cdot$ radicals[27] provides a ready termination. The competition between propagation (eq 2) and cleavage (eq 7) depends on the concentration of hydroperoxide (essential for propagation) and the effect of reaction medium on cleavage. Cleavage is least favored in the gas phase[14] and most favored in polar hydroxylic solvents without reactive hydrogen atoms.[14,28]

(26) Assuming $k_{24} = 10^7$ based on 2*t*-$BuO\cdot$ reacting $^1/_{10}$th as fast as they escape from the solvent cage.

(27) R. Hiatt and T. G. Traylor, unpublished work.

(28) J. D. Bacha and J. Kochi, *J. Org. Chem.*, **30**, 3272 (1965).

Two examples illustrate the application (really the foundation) of these generalizations. In experiments at about the same t-BuO_2H–t-Bu_2O_2 ratio, chain lengths in the decomposition of hydroperoxide are about the same at 100° in the gas phase (run 65D in Table VI) and in benzene solution (0.0196 M t-Bu_2O_2 experiment in Table III). Despite the 4-fold higher concentrations in solution, 10–30% of the t-BuO· radicals cleave compared to only 5–10% in the gas phase. At higher concentrations of t-BuO_2H cleavage of t-BuO· radicals becomes unimportant compared to propagation, and the kinetics and the products change and resemble the liquid phase reaction at 45°.

Registry No.—t-BuO_2H, 75-91-2; *sec*-Bu_2O_2, 4715-28-0; t-$BuO_2C_6H_{11}$, 15619-54-2.

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Homolytic Decompositions of Hydroperoxides. III.[1a,b] Radical-Induced Decompositions of Primary and Secondary Hydroperoxides

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Radical-induced decompositions of primary and secondary hydroperoxides at 45° in benzene have chain lengths of 0.7–1.4. However, at 100° in benzene solution or in the gas phase the reaction is more complex, involving both peroxy and carbon radicals, and gives little or no oxygen. At 45° alkoxy radicals preferentially attack the peroxy hydrogen atom instead of the hydrogen in these peroxides; at 100° attack must occur on both positions. Interactions of two nontertiary peroxy radicals are almost always terminating. They appear to react mostly by a concerted, nonradical decomposition of intermediate R_2O_4.

Primary or secondary hydroperoxides are intermediates in many important autoxidations such as those of toluene, tetralin, and cyclohexane. The routes by which these are decomposed to useful products are of more general interest than the reactions of tertiary hydroperoxides described in part II.[1b] We expected that free-radical-induced decompositions of primary and secondary hydroperoxides would differ from those of tertiary hydroperoxide for two reasons. (1) Terminating interactions by disproportionation of two primary or secondary peroxy radicals appear to be much faster[2,3] than interactions of two tertiary peroxy radicals. Therefore chain lengths of decompositions involving the former peroxy radicals should be short (eq 12). (2) To the extent that α-hydrogen atoms

$$2R_1R_2HCO_2\cdot \longrightarrow R_1R_2HCOH + R_1R_2C{=}O + O_2 \quad (12)$$

in primary and secondary hydroperoxides rather than the peroxy hydrogen atoms are abstracted, then hydroxyl radicals may become the chain carrier (eq 6). This report describes decompositions of *n*-butyl,

$$R_1R_2HCO_2H + \cdot OH \longrightarrow (H_2O +)R_1R_2\dot{C}O_2H \longrightarrow R_1R_2C{=}O + OH \quad (6)$$

sec-butyl, 3-cyclopentenyl, and α-tetralyl hydroperoxides by DBPO in benzene at 45° and of *sec*-butyl hydroperoxide by t-Bu_2O_2 in benzene and in the gas phase at 100°.

Experimental Section

α-Tetralyl and cyclopentenyl hydroperoxides were prepared by air oxidation of the hydrocarbons and respectively recrystallized or vacuum distilled to 95+ % purity (by reflux iodometric titration, part II[1b]). *n*-BuO_2H (92%) and *sec*-BuO_2H (94+%) were prepared by the methods of Mosher and coworkers.[4] Other materials, analytical procedures, and procedures for decompositions were as described in part II.[1b]

t-BuO·-Induced Decompositions of *p*- and *sec*-Hydroperoxides in Benzene at 45 and 100°

The results with t-BuO_2H in part II[1b] raised the question of whether interaction of two primary or secondary solvent peroxy radicals would also produce alkoxy radicals (eq 3, part I[1a]) capable of continuing the chain. Radical-induced decompositions of primary and secondary hydroperoxides in benzene were therefore investigated.

Table I shows chain lengths, *i.e.*, $-\Delta[RO_2H]/-\Delta 2[\text{initiator}]$, and products of the DBPO-induced decompositions of one primary and three secondary hydroperoxides in benzene at 45°; oxygen evolution, where measured, was 75–80% of theory for *sec*-BuO_2H. For 3-cyclopentenyl and *sec*-butyl hydroperoxides, the only ones for which the kinetics were measured, $-d[RO_2H]/dt \propto [\text{DBPO}]$. The over-all result corresponds to

TABLE I

DBPO-INDUCED DECOMPOSITION OF PRIMARY AND SECONDARY HYDROPEROXIDES IN BENZENE[a] AT 45°

RO_2H	$[RO_2H]_0$, M	$[DBPO]_0$, M	Chain length[b]	—Products, %— ROH[c]	R=O[d]	O_2
n-Butyl	0.217	0.0862	0.70	53	14[e]	
sec-Butyl	0.272	0.098	1.0	50	46	
sec-Butyl	0.221	0.118	0.9			76
3-Cyclopentenyl	0.124	0.0100	0.72			
α-Tetralyl	0.092	0.055	0.72			

[a] Solutions were degassed, sealed in ampoules, and heated for 450 min or ten half-lives of the initiator. [b] Corrected for cage effect of DBPO; *cf.* part II.[1b] [c] Alcohol from R, based on decomposed RO_2H. [d] Aldehyde or ketone from R, based on decomposed RO_2H. [e] Also butyric acid, not determined quantitatively.

(1) (a) Part I: R. Hiatt, J. Mill, and F. R. Mayo, *J. Org. Chem.*, **33**, 1416 (1968). Equations 1–16 appear in part I. Part II: R. Hiatt, T. Mill, K. C. Irwin, and J. K. Castleman, *ibid.*, **33**, 1421 (1968). Equations 17–24 appear in part II. (c) To whom all correspondence should be addressed at Brock University, St. Catherines, Ontario, Canada.

(2) G. A. Russell, *J. Amer. Chem. Soc.*, **77**, 4583 (1955).

(3) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **44**, 1119 (1966).

(4) F. Welch, H. R. Williams, and H. S. Mosher, *J. Amer. Chem. Soc.*, **77**, 551 (1955).

TABLE II

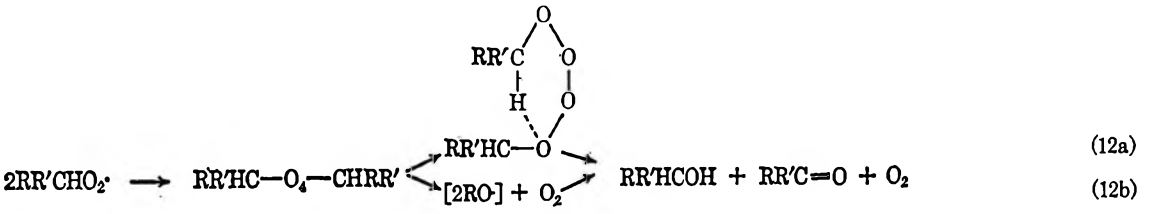
t-Bu_2O_2-INDUCED DECOMPOSITION OF *sec*-BuO_2H IN BENZENE AT 100°

Time, min	Reactants, mol/l. [*sec*-BuO_2H]$_0$	Reactants, mol/l. [*t*-Bu_2O_2]$_0$	% RO_2H decomposed	Chain length[a]	Products,[b] % *sec*-BuOH	Products,[b] % AcEt	Products,[b] % O_2
4025	0.187	0	4				
2671	0.183	0.186	39	0.98	65	35	
2838	0.184	0.180	39	1.5[c]	0	35	0.1
2890	0.180	0.177	45	1.4	44	48	2
7202	0.180	0.177	71	1.1	35	41[d]	

[a] Calculated from measured changes in concentrations of both peroxides. [b] As percentage of hydroperoxide decomposed. [c] Calculated from $\Delta RO_2H/\Delta t$-BuOH. [d] Also 4% acetaldehyde and 13% acetic acid.

eq 12 plus some oxidation by the oxygen evolved of the alcohol and aldehyde formed.

Although about 5% *t*-Bu_2O_2 based on decomposed DBPO originates by cage recombination of *t*-BuO· radicals from DBPO, no *sec*-Bu_2O_2 could be detected when the decomposition products from *sec*-BuO_2H were examined by combined fractional distillation and infrared techniques. *sec*-Bu_2O_2 (2.5%) *was* found when 0.3 *M* *sec*-BuO_2H in benzene was completely decomposed by cobaltous octoate and the products were analyzed by flame ionization gas chromatography.



If our interpretation of metal-catalyzed decompositions is correct (part IV), the yield from radical-induced decompositions should be about 3%.

Of greater interest was the behavior of a primary or secondary hydroperoxide at 100° where several corresponding hydrocarbons have been oxidized. *sec*-Butyl hydroperoxide was chosen for this purpose, and some results of rate measurements and product analyses are presented in Table II.

These experiments at 100° are characterized by erratic ketone–alcohol ratios and chain lengths and essentially no oxygen production. Since the products found in Table II exclude the possibility of reaction of much of the expected oxygen, some of the analyses must be faulty; *e.g.*, some other hydroperoxide may have replaced *sec*-BuO_2H in the titration.

Decompositions of *sec*-BuO_2H at 100° in the Gas Phase

In the gas phase at 100°, 9–19% of 0.009 *M* *sec*-BuO_2H decomposed in 15 hr in Pyrex *in the absence of free-radical initiators.* This erratic thermal decomposition, about twice as fast as for *t*-BuO_2H in similar circumstances,[2] was reduced to about one-fifth that rate (9–16% in 70 hr) by adding 5 atm of ethane, which is practically inert to alkoxy radical attack at 100°.

With 0.006 *M* added *t*-Bu_2O_2, the rates of disappearance of 0.004 *M* *sec*-BuO_2H (in 5 atm of ethane) were considerably faster than in the absence of initiator (80–90% in 70 hr) and chain lengths estimated from $\Delta RO_2H/\Delta t$-BuOH were 2.7–3 for four replicate runs. Ketone–alcohol ratios were 1.6 : 3; material balances on *sec*-butyl groups were generally low by 25%, and, where measured, only 27 and 0% oxygen were found.

Discussion

One of the major objectives of this work was to gain some detailed knowledge about the extent to which interactions of primary and secondary peroxy radicals lead to termination *via* a concerted Russell-type mechanism[5] (eq 12a) or by disproportionation of caged alkoxy radicals (eq 12b).

The short chain lengths at 45° (0.7–1.0) establish only that no measurable proportion of *free* radicals is produced in eq 12 at this temperature. The good oxygen yield and close to 50% yields of alcohol from primary and secondary hydroperoxides in benzene at 45° are also consistent with eq 12 (without distinguishing between 12a and 12b) but not with any important contribution from eq 6. Thus, the DBPO-induced decomposition at 45° occurs (as for tertiary hydroperoxides) by abstraction of the peroxy hydrogen atom,[6] and nearly every interaction of the resulting primary or secondary peroxy radicals leads to termination, in marked contrast to interactions of tertiary peroxy radicals which terminate only once in eight to ten interactions at 45°.[7]

In the 100° decompositions, particularly in the gas phase, the chain lengths exceed unity and the ketone–alcohol ratios are higher than at 45°. All the material balances at 100° are unsatisfactory. At 45°, the DBPO decomposes rapidly and the relatively high concentration of *sec*-BuO_2 · radicals favors their interaction (eq 12). At 100°, the *t*-Bu_2O_2 decomposes very slowly, apparently favoring reactions which are first order in *sec*-BuO_2· [induced oxidation of peroxide decomposition products or attack of the α C–H bond in *sec*-BuO_2H

(5) G. A. Russell, *J. Amer. Chem. Soc.*, **79**, 3871 (1957).

(6) The chain lengths of less than one found for *n*-butyl cyclopentenyl, and tetralyl hydroperoxides probably arise from attack of some RO· radicals on allylic hydrogens in the latter two cases and on product *n*-PrCHO from *n*-BuO_2H. The radicals thus produced may terminate without destroying hydroperoxide and lead to waste of initiator.

(7) R. Hiatt, J. Clipsham, and T. Visser, *Can. J. Chem.*, **42**, 2754 (1964).

(with formation of ketone as in eq 6)]. Because of the apparent intrusion of a reaction such as eq 6, we do not yet know whether to attribute any of the increased chain length at 100° to escape of free RO· radicals from eq 12b. Clarifying experiments are in progress.

Registry No.—*n*-BuO_2H, 4813-50-7; *sec*-BuO_2H, 13020-06-9; α-tetralyl hydroperoxide, 771-29-9.

Homolytic Decompositions of Hydroperoxides. IV.[1a-c] Metal-Catalyzed Decompositions

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t-Butyl hydroperoxide has been decomposed by a variety of cobalt salts and compounds of other metals (Fe, V, Mn, Ce, and Pb). In chlorobenzene or alkanes at 25–45° half-lives for decomposition of 0.1 *M* *t*-BuO_2H by 10^{-4} *M* catalyst ranged from 1 to 10 min. Products included approximately 88% *t*-BuOH, 11% *t*-Bu_2O_2, 1% acetone, and 93% O_2. Decompositions in alcohol–chlorobenzene mixtures yielded more acetone but were only *ca.* one-hundredth as fast as in pure chlorobenzene. Reactions in all solvents were subject to autoretardation owing partly to formation of aldehydes and carboxylic acids and partly to changes in the catalyst which caused its eventual precipitation. Decompositions of α-cumyl, *n*-butyl, and *sec*-butyl hydroperoxides were normally one-fourth to one-tenth as fast as those of *t*-BuO_2H. *n*-BuO_2H and *sec*-BuO_2H yielded 70% O_2 and the corresponding alcohol and aldehyde or ketone in a ratio of about 2. The results suggest that these reactions are essentially the same as free-radical-induced decompositions but are initiated by metal ion–hydroperoxide interactions. Generally speaking the choice of metal ion, as long as it can undergo a facile one-electron redox reaction, has little influence on either products or rates of decomposition except in the presence of olefins.

Metal ion catalyzed decompositions of hydroperoxides are important in metal ion catalyzed autoxidations of hydrocarbons. While it is generally agreed that these autoxidations are initiated by radicals generated from ion hydroperoxide interactions,[2,3] the interactions themselves and the mechanisms by which useful products arise from the hydroperoxides are poorly understood despite numerous investigations.[4] This report shows how metal-catalyzed decompositions are related to free-radical-induced decompositions (parts II[1b] and III[1c]). Only about a third of our experiments are reported.

Experimental Section

Materials.—Hydroperoxides and chlorobenzene were obtained and purified by the methods described in parts II[1b] and III.[1c] *n*-Pentane, cyclohexane, *n*-heptane, and 2,2,4-trimethylpentane were Matheson Coleman and Bell "Chromatograde" reagents, refluxed for 6 hr over CaH_2 and distilled.

Cobaltous stearate ($CoSt_2$) and cobaltous 2-ethylhexanoate ($CoOct_2$) were prepared by the methods of Dyer[5] and of Vold.[6] An aqueous solution of the sulfate was added to a neutralized ethanol solution of the carboxylic acid and the precipitate was collected and dried at 90° in vacuum. Infrared absorptions of the compounds at 1708 cm^{-1} revealed that they contained 15–20% of the free carboxylic acid, as did the cobaltous stearate obtained from K & K Laboratories. Two reprecipitations of the salts with acetone from a hexane solution gave acid-free catalysts (less than 0.5%) of decreased solubility in chlorobenzene and a higher then theoretical amount of cobalt (Table I). Cobaltic stearate ($CoSt_3$), prepared by treatment of a solution of $CoSt_2$ in acetic and stearic acids with an excess of H_2O_2, also contained free acid which was removed as above.

TABLE I
ANALYSES OF REPRECIPITATED COBALT SALTS

Salt	% cobalt: Experimental[a]	Theory
Cobaltous laurate	15.05	12.88
Cobaltous stearate	10.59	9.42
Cobaltous 2-ethylhexanoate	20.50	17.06
Cobaltic stearate	14.04	6.89
$CoCO_3$[b]	49.08	49.55

[a] Analyses were by West Coast Analytical Laboratory by both polarography and reduction to metal. [b] Baker reagent grade.

The high percentage of cobalt in these compounds indicated their formula to be $[Co(RCO_2)_2]_x[Co(RCO_2)(OH)]_y$.[6] The analysis of the cobaltic stearate showed it to be nearer CoOSt than $CoSt_3$.

Cobaltous acetylacetonate (CoA_2) was obtained from K & K Laboratories and dried at 60° under vacuum. Cobaltic acetylacetonate (CoA_3) was prepared by oxidation of the cobaltous salt with H_2O_2 in the presence of excess acetylacetone and recrystallized. V^{III}, Fe^{III}, Ni^{II}, Mn^{II}, and Ce^{II} acetylacetonates, vanadous octoate, and cobalt salicylalethylenediimine were obtained from K & K Laboratories and used without further purification.

Iron phthalocyanine (FePCN) was obtained from the Pigment Colors Division of Du Pont.

Lead naphthenate ($PbNap_2$) manganous octoate, and cupric octoate were Nuodex solutions, 24, 8, and 8%, respectively, by weight in metal.

Procedures.—Reactions in mixtures of chlorobenzene with protic solvents were started by syringing 0.2–3 ml of neat hydroperoxide into 20 ml of the catalyst-containing solution immersed in a constant-temperature bath. Reactions in alkanes were refluxed to exclude oxygen from the air and expel that produced by the peroxide decomposition. Flasks were immersed in a bath 10–15° warmer than the reflux temperature of the solvent. Boiling chips were used to minimize superheating.

Rates of decomposition were measured by pipetting aliquots into a stop bath of 1:10 AcOH–*i*-PrOH and determining residual hydroperoxide by reflux iodometric titration (part II[1b]).

For most analyses of products a gas chromatograph with thermal conductivity sensing was used. Columns were packed with a 20% loading of Carbowax 20M or didecyl phthalate on Chromosorb P. Residual hydroperoxides were reduced to al-

(1) Part I: R. Hiatt, T. Mill, and F. R. Mayo, *J. Org. Chem.*, **33**, 1416 (1968). Equations 1–16 appear in part I. (b) Part II: R. Hiatt, T. Mill, K. C. Irwin, and J. K. Castleman, *ibid.*, **33**, 1421 (1968). Equations 17–24 appear in part II. (c) Part III: R. Hiatt, T. Mill, K. C. Irwin, and J. K. Castleman, *ibid.*, **33**, 1428 (1968). Equations 12a and b appear in part III. (d) To whom all correspondence should be addressed at Brock University, St. Catherines, Ontario, Canada.

(2) N. Uri, *Nature* **177**, 1177 (1956).

(3) E. T. Denisov and N. M. Emanuel, *Usp. Khim.*, **29**, 1409 (1960).

(4) Reference 3 contains a useful summary of work to 1960. This report considers some more recent investigations.

(5) E. Dyer, K. R. Carle, and D. E. Weiman, *J. Org. Chem.*, **23**, 1464 (1958).

(6) R. D. Vold and G. S. Hattiangdi, *Ind. Eng. Chem.*, **41**, 2311 (1949).

cohols with triphenylphosphine (Ph_3P) before analysis; unreduced dialkyl peroxides, except t-Bu_2O_2, were decomposed to mixtures of alcohols and ketones in the column. Dialkyl peroxides were preserved on columns with only 2% loading of didecyl phthalate, and were analyzed using a chromatograph with flame ionization detection. Evolved gases were trapped and analyzed by a mass spectrometer.

Decompositions in Chlorobenzene

t-Butyl Hydroperoxide Rates and Products.—t-BuO_2H (0.1–0.2M) in chlorobenzene at 25° was entirely decomposed by millimolar amounts of a variety of catalysts including cobaltous stearate, 2-ethylhexanoate, acetylacetonate, and salicylalethylenediimine, cobaltic stearate, iron phthalocyanine, acetylacetonates of V^{III}, Mn^{II}, Ce^{IV}, and Nuodex preparations (octoates or naphthenates) of Co^{II}, Mn^{II}, Pb^{II}, and V^{III}. Times for decomposition in Table II varied from a few minutes for cobalt carboxylates or FePCN to several days for cobaltous salicylalethylenediimine or Pb napthenate (at 50°). Each mole of the more active catalysts decomposed more than 1000 mol of hydroperoxide before becoming deactivated.

TABLE II

RATES AND PRODUCTS OF METAL ION CATALYZED DECOMPOSITIONS OF 0.1 M t-BuO_2H IN CHLOROBENZENE

Temp, °C	Catalyst	Concn, mM	$t_{1/2}$, min	Products, %[a] t-BuOH	t-Bu_2O_2	AcMe
22.7	$CoSt_3$	26	27	86.6	12.7	0.5
25	$CoOct_2$	10	5	87.8	11.8	0.5
25	FePCN	4.7	7	84.7	14.6	1
25	CoA_2	500	14	87.8	11.5	0.5
25	CoSal	71	366	85.1	13.7	1
25	$CoOct_2$ / HOAc	10 / 3.5	10	86.5	13.1	0.5
45	$CoSt_3$	6.5	7.5	89.3	9.2	1.5
45	$CoSt_3$	26	2.1	89.4	9.1	1.5
45	$CoSt_3$	190	<0.3	88.6	9.8	1.5
45	$CoOct_2$	10	1.3	89.0	8.8	2
50	$PbNap_2$	265	250	88.7	9.2	2

[a] Mole % based on t-BuO groups found. Total t-BuO products found ranged from 96 to 102% of t-BuO_2H decomposed.

At room temperature cupric octoate (Nuodex solution) and the acetylacetonates of Ni^{II}, Co^{III}, and Fe^{III} were inert[7] toward t-BuO_2H. FeA_2 decomposed only half a mole of hydroperoxide per mole of catalyst.

The products of the chain decompositions (Table II) at 25° were approximately 86% t-BuOH, 12% t-Bu_2O_2, 0.5% acetone, and 93% O_2 (based on $^1/_2$ O_2 from each t-BuO_2H), independent of the catalyst or the rate of decomposition. No methanol was found. Glpc analysis indicated some formaldehyde (not estimated quantitatively); Dean and Skirrow[8] found 3.8% under similar conditions. Decompositions at 45° gave only 9% t-Bu_2O_2, although this peroxide was stable under the conditions of the reaction.

Kinetics of Decomposition.—Some autoretardation occurred in all decompositions, but the least occurred in reactions catalyzed by cobalt carboxylates or iron phthalocyanine. For the latter, plots of log [t-BuO_2H] *vs.* time were linear to at least 70% decomposition, with slopes proportional to catalyst concentration. With [t-BuO_2H]$_0$ varied from 0.05 to 0.5 M and with 0.01 to 0.45 mM catalyst, the rate expression was first order in each reactant within experimental error (eq 25 where

$$-d[t\text{-}BuO_2H]/dt = k_2[t\text{-}BuO_2H][M] \quad (25)$$

M = $CoSt_2$, $CoSt_3$, $CoOct_2$ or FePCN). Table III shows the second-order rate constants[9] and over-all activation energies for these catalysts. The rate constants for $CoSt_2$ and $CoSt_3$ were very similar; the rate at which a solution initially containing $CoSt_2$ or $CoSt_3$ became a steady-state equilibrium mixture of cobaltous and cobaltic (indicated by the color change on addition of t-BuO_2H) was too fast to measure using a Cary spectrophotometer. For $CoOct_2$ in chlorobenzene, Richardson[10] has shown the equilibrium to be about 55% cobaltous and 45% cobaltic. FePCN also underwent a rapid color change from deep green to light yellow.

TABLE III

RATE CONSTANTS AND ACTIVATION ENERGIES FOR DECOMPOSITIONS OF HYDROPEROXIDES IN CHLOROBENZENE

Temp, °C	R in RO_2H[a]	Catalyst[b]	k_2[c]	E_a
25.0	t-Bu	$CoOct_2$	23.2 ± 1.5	12
45.0			81.6 ± 5.5	
22.7		$CoSt_3$	1.66[d]	22
45.0			21.9 ± 1.1	
45.0		$CoSt_2$	17.1 ± 1.2	
0.0		FePCN	11.0 ± 0.8	9
22.5			37.7 ± 0.1	
23.5	n-Bu	$CoOct_2$	5.2[d]	
45.0		$CoSt_3$	3.1 ± 0.2	
45.0	α-Cumyl	$CoOct_2$	21[d]	

[a] Initial [RO_2H] varied from 0.05 to 0.5 M. [b] [Catalyst] varied from 0.013 to 0.45 mM. [c] Second-order rate constants (eq 25) in units of liter/mole/second. [d] Only one run.

Decompositions catalyzed by CoA_2 gave curved plots of log [t-BuO_2H] *vs.* time. The sharp decrease in initial rate had no orderly relationship to decreasing [t-BuO_2H] but was related to the oxidation of the initial cobaltous complex to the apparently much less active CoA_2^+. Determining Co^{II} concentrations spectrophotometrically, and rates and hydroperoxide concentration titrimetrically from parallel runs, gave a rate expression

$$-d[t\text{-}BuO_2H]/dt = k[t\text{-}BuO_2H][Co^{II}]^{1/2}$$

Retarders and Autoretardation.—Decompositions were retarded by addition of millimolar amounts of materials which strongly complex metal ions. These included carboxylic acids, aldehydes, EDTA, triethylenetetramine, 1,10-phenanthroline, and acetylacetone. Some typical effects are shown in Table IV. O_2, H_2O, and 0.1 M t-BuOH were not retarders (although the fading of the deep blue color of $CoOct_2$ solutions on addition of H_2O indicated aquation of the complex). Ionol (2,6-di-t-butyl-p-cresol) retarded FePCN-cata-

(7) Cuprous salts, of course, do reduce hydroperoxides [J. K. Kochi, *J. Amer. Chem. Soc.*, **85**, 1958 (1963)] and can give long-chain decompositions if alkyl radicals are present in the system to reduce Cu^{II} back to Cu^{I}. Richardson [*ibid.*, **88**, 975 (1966)], while confirming our results at 25°, has shown that cupric octoate will oxidize hydroperoxides at 50°.

(8) M. H. Dean and G. Skirrow, *Trans. Faraday Soc.*, **54**, 849 (1958).

(9) The approximately 10% uncertainty in these constants was entirely random and apparently resulted from adventitious impurities. In one instance careless handling of the PhCl solvent caused reactions in it to proceed about half as fast as usual. Ordinarily rates were fairly reproducible and are in good agreement with those of Richardson.[10]

(10) W. H. Richardson, *J. Amer. Chem. Soc.*, **87**, 1096 (1965).

TABLE IV

EFFECTS OF RETARDERS ON DECOMPOSITIONS OF 0.1 *M* *t*-BuO_2H IN CHLOROBENZENE

Retarder	Concn, m*M*	k_1[a] × 10^4, sec^{-1}
0.1 m*M* $CoOct_2$ at 25°		
None		2.3
HOAc	3.2	1.1
CF_3CO_2H	3.6	0.66
EDTA[b]	*c*	<0.1
PrCHO	10	~0
0.08 m*M* $CoSt_2$ at 45°		
None		1.4
Stearic acid	44	0.5
HOAc	5.4	1.0
1,10-Phenanthroline	13	0.5
Triethylenetetramine	6	0.18

[a] Pseudo-first-order rate constant. [b] Ethylenediamine–tetraacetic acid disodium salt. [c] PhCl solution of $CoOct_2$ shaken with the solid disodium salt and filtered before addition of *t*-BuO_2H.

lyzed decompositions but not those catalyzed by cobalt compounds.

The autoretardation of normal runs which occurred after 60–80% decomposition (prior to visible catalyst precipitation) was caused partly by formation of carboxylic acids (detected by ir analysis of reclaimed catalysts initially acid-free) and partly by unidentified volatile products, which, if acidic, were in too low a concentration to be detected by ir analysis or titration. Probably a third factor was decrease in catalyst solubility during the runs, although precipitation of the catalyst was usually not evident until several hours after decomposition was complete.

Other Hydroperoxides.—Reactions catalyzed by $CoSt_3$ or $CoOct_2$ showed that *n*-BuO_2H decomposed about one-eighth as fast and α-cumyl hydroperoxide about one-fourth as fast, respectively, as *t*-BuO_2H in chlorobenzene (Table III). Reactions of *n*-BuO_2H were strongly autoretarded by formation of *n*-PrCHO (or butyric acid if O_2 was not swept out).

Discussion.—A distinction must be made between catalytic decomposition, in which each metal ion decomposes many hundreds of hydroperoxide molecules, and what we shall label stoichiometric reactions, in which the ratio is nearer 1:1. Catalytic decompositions, typified here by reactions initiated by cobalt carboxylates or iron phthalocyanine, seem fairly simple. The uniformity of products and the bimolecular rate expressions suggest a radical-induced decomposition of the usual type initiated by metal ion–hydroperoxide interactions. The reactions in eq 13 and 14 are widely accepted[3] where M is a metal ion and

$$M^n + RO_2H \longrightarrow M^{n+1} + RO\cdot + OH^- \quad (13)$$

$$M^{n+1} + RO_2H \longrightarrow M^n + RO_2\cdot + H^+ \quad (14)$$

ligands. Catalyst dimers and hydroperoxide complexes are temporarily left in abeyance. If this is followed by an induced chain (eq 2, 3, and 4 in part I[1a]), an expression for disappearance of hydroperoxide can be developed (eq 26). Assuming a steady state for RO·

$$-d[RO_2H]/dt = k_{13}[RO_2H][M^{II}] + k_{14}[RO_2H][M^{III}] + k_2[RO\cdot][RO_2H] \quad (26)$$

and rapid cycling of the metal ion, eq 27 and 28 apply.

$$k_{13}[RO_2H][M^{II}] = k_{14}[RO_2H][M^{III}] \quad (27)$$

$$-d[RO_2H]/dt = (2k_3/k_4 + 3)[M^{II}][RO_2H] \quad (28)$$

Since $M^{II} + M^{III} = M_0$, eq 29 can be written.

$$\frac{-d[RO_2H]}{dt} = (2k_3/k_4 + 3)\frac{k_{13}k_{14}}{k_{13} + k_{14}}[M]_0[RO_2H] \quad (29)$$

For *t*-BuO_2H decompositions, k_3/k_4, the induced chain length after initiation, can be calculated from the ratio of alcohol and peroxide products, since the relationship in

$$2k_3/k_4 + 3 = \frac{[t\text{-BuOH}]_f + [\text{acetone}]_f}{[t\text{-Bu}_2O_2]_f} \quad (30)$$

eq 30 exists where f indicates final concentration. From typical examples in Table II, $k_3/k_4 = 8.8$ at 45° (in good agreement with results from DBPO-induced decompositions) and 6.0 at 25°. This ratio can now be used to calculate the expected yield of O_2 (not 100%, since each initiating cycle produces a molecule of H_2O) (eq 31).

$$\%\ O_2 = 100(2k_3/k_4 + 2)/(2k_3/k_4 + 3) = 95\% \text{ at } 45° \quad (31)$$

The slower rates of decomposition of *n*-BuO_2H and α-cumyl O_2H agree well with their shorter induced chain lengths.

The kinetic simplicity of the decompositions in PhCl (excluding those catalyzed by $CoAc_2$ which will be discussed later) makes a more complex scheme unnecessary. Catalyst dimers or higher aggregates, proposed by some workers[10–12] to explain the complex kinetics found in other solvents, probably obtain in chlorobenzene.[10] However, the degree of aggregation must remain fairly constant over the concentration range used. Complexing between catalyst and hydroperoxide[8,10,12] may occur prior to eq 13 and 14, but it appears to have no important consequences other than the retardation caused by other materials which also form strong complexes with the catalyst.[13–15]

The apparent unimportance of metal ion reactions with alkoxy or peroxy radicals in our experiments must be largely due to the low concentrations of the catalyst. Much larger concentrations are needed to reveal such reactions.[16,17] However, the stoichiometry of the FeA_2–*t*-BuO_2H reaction is probably explained by eq 32 rapidly

$$t\text{-BuO}\cdot + FeA_2 \longrightarrow FeA_2^+ + t\text{-BuO}^- \quad (32)$$

following eq 13 (Fe^{III} is inert to hydroperoxides). Cobaltous ion appears to react with *t*-BuO· much less rapidly. Decompositions of *t*-BuO_2H under conditions where only one valence state of cobalt is active [$Co(OAc)_3$ in HOAc at 25° or K_2Co EDTA in HOAc–H_2O][8,11a] have approximately 1:1 stoichiometry. Apparently under these conditions RO_2H competes effectively with Co^{II} for RO·.

Decompositions in Other Solvents

Some metal-catalyzed decompositions were carried out in alkanes and in alcohol–chlorobenzene mixtures.

(11) (a) W. H. Richardson, *J. Amer. Chem. Soc.*, **87**, 247 (1965); (b) W. H. Richardson, *J. Org. Chem.*, **30**, 2804 (1965).

(12) Y. Kamiya, S. Beaton, A. Lafortune, and K. U. Ingold, *Can. J. Chem.*, **41**, 2020 (1963).

(13) This complexing probably accounts for the effect of Ionol as well. Phenols have been shown to complex strongly with phthalocyaninelike compounds.[14] Ionol should not affect the radical chain since galvanoxyl, a radical similar to the one produced from Ionol, attacks *t*-BuO_2H to give the usual induced decomposition.[15]

(14) P. George, R. L. J. Lyster, and J. Bettlestone, *J. Biol. Chem.*, **236**, 3246 (1961).

(15) J. C. McGowan and T. Powell, *J. Chem. Soc.*, 238 (1960).

(16) J. K. Kochi, *J. Amer. Chem. Soc.*, **84**, 1193 (1962).

(17) W. J. deKlein and E. C. Kooyman, *J. Catal.*, **4**, 626 (1965).

TABLE V

METAL-CATALYZED DECOMPOSITIONS OF 0.1–0.3 *M* HYDROPEROXIDES IN REFLUXING ALKANES

R in RO_2H	Concn of catalyst, m*M*	$[k_1]_0$,[a] sec^{-1}	Products, % ROH[a]	R=O[b]	R_2O_2[b]	S—OH[c]	S=O[c]	O_2
With $CoOct_2$ in *n*-Pentane at 37.8°								
t-Bu	6.4	0.011	91		8	9	6	90
sec-Bu	6.4	0.0011						
sec-Bu	25	0.0055	61	36	3			70
n-Bu	25	0.0055	67	33				70
With $CoOct_2$ in Cyclohexane at 81.5°								
t-Bu	5.7	0.021	88	2	11[d]	22	14	22
α-Cumyl	6.5	0.020	95	5		31	16	
sec-Bu	6.5	0.0053	50	40		12	8	
n-Bu	6.3	0.0052	65	24		16	5	
With $CoOct_2$ except as Noted[e–f] in *n*-Heptane at 98.6°								
t-Bu	6.5	>0.037						
t-Bu	5.6	>0.024						
sec-Bu	6.5	0.01	49	31				
sec-Bu	81		64	27				
sec-Bu	12[f]	0.004	63	23				
sec-Bu	14[g]	0.0007	45	42				

[a] First-order rate constants calculated from time for 5% decompositions. [b] Alcohol, ketone or aldehyde, or dialkyl peroxide from hydroperoxide in mole % based on RO groups found. [c] Alcohol or ketone from solvent. [d] $C_6H_{11}O_2$-*t*-Bu. [e] CoA_2. [f] $MnOct_2$. [g] $VOct_3$.

We reasoned that metal ions might play a more varied and influencial role in these media, where radical-induced chains are short, than in pure chlorobenzene. Reactions in alkanes were refluxed to expel O_2 and prevent autoxidation.

Decompositions in Refluxing Alkanes. Decompositions in *n*-Pentane.—Decompositions of *n*-BuO_2H, *sec*-BuO_2H, and *t*-BuO_2H by 0.1 m*M* $CoOct_2$ in refluxing pentane at 38° differed little in initial rates or products (Table V) from comparable decompositions in chlorobenzene. Rate expressions were first order in hydroperoxide and apparently second order in cobalt at concentrations of $CoOct_2$ that were <0.1 m*M* but tended to lesser dependence at higher concentrations. Initial rates for *t*-BuO_2H were only one-eighth as fast when 1.6 *M* cumene was added.

Decompositions of *t*-BuO_2H showed severe autoretardation. Plots of $1/[RO_2H]^2$ against time were linear, giving the appearance of a third-order reaction in hydroperoxide. However, inital rates (calculated from the reciprocal square plots) were proportional to $[RO_2H]_0$. We suspect that a similar autoretardation is the basis for Dyer's claim[5] that decompositions of tetralin hydroperoxide by $CoOct_2$ in cyclohexane are second order in hydroperoxide, and that these reactions are really first order.

Decompositions in Higher Boiling Alkanes.—In refluxing cyclohexane, *n*-heptane, or trimethylpentane, kinetic analysis of *t*-BuO_2H decompositions was precluded by both very rapid decomposition and rapid deactivation of the catalyst. In a typical cyclohexane run, with 0.1 *M* *t*-BuO_2H and 0.057 m*M* $CoOct_2$, 44% of the hydroperoxide was decomposed in the first 20 sec (the minimum time necessary to remove a sample for titration) and only 12% more decomposed during the next 30 min. More catalyst added at this point was instantly deactivated with only slight reduction of hydroperoxide concentration. Decompositions of α-cumyl O_2H were also strongly autoretarded. Estimates of initial rates (Table V) for these hydroperoxides are almost certainly low. Decompositions of *n*-BuO_2H and *sec*-BuO_2H were slower initially but showed little autoretardation.

The product distribution (where measured) was relatively insensitive to the nature of the catalyst. Table V shows that $CoOct_2$, $MnOct_2$, and $VOct_3$ all gave about the same proportions of *sec*-BuOH and methyl ethyl ketone from *sec*-BuO_2 in refluxing *n*-heptane.

Significant yields of oxidized solvent molecules were obtained. These were most carefully investigated for reactions of *t*-BuO_2H in cyclohexane, where they accounted for about half of the oxygen liberated from decomposed hydroperoxide.

Products listed in Table V are a composite from several runs analyzed by different methods and fully described in part II.[1b] In most analyses the mixed peroxide pyrolyzed and only alcohol and ketone were observed. Water was not measured quantitatively. It probably accounts for that oxygen not found elsewhere. Products of runs not carried to completion probably contained some cyclohexyl hydroperoxide. (Glpc analyses of product mixtures in which residual hydroperoxide had been reduced to alcohol by Ph_3P gave more cyclohexanol and less cyclohexanone than analyses in which residual hydroperoxide was pyrolyzed in the chromatograph.)

Discussion.—The products of decompositions in *n*-pentane agree nicely with the scheme proposed for reactions in chlorobenzene, modified slightly by some radical attack on solvent. For *t*-BuO_2H such attack produces somewhat shorter induced chains, lower yields of O_2 and *t*-Bu_2O_2, and some products of pentane oxidation. The relations shown in eq 13, 14′, 2, and 12 suggest that in decompositions of *sec*-BuO_2H and *n*-BuO_2H, the yields of alcohol, ketone, or aldehyde, and O_2 correspond to decomposition of three peroxide molecules per metal cycle (eq 33).

$$\text{sec-BuO}_2\text{H} + \text{M}^{\text{II}} \longrightarrow \text{sec-BuO}\cdot + \text{M}^{\text{III}} + \text{OH}^- \quad (13)$$

$$\text{sec-BuO}_2\text{H} + \text{M}^{\text{III}} + \text{OH}^- \longrightarrow \text{sec-BuO}_2\cdot + \text{M}^{\text{II}} + \text{H}_2\text{O} \quad (14')$$

$$\text{sec-BuO}\cdot + \text{sec-BuO}_2\text{H} \longrightarrow \text{sec-BuOH} + \text{sec-BuO}_2\cdot \quad (2)$$

$$2sec\text{-}BuO_2\cdot \longrightarrow sec\text{-}BuOH + AcEt + O_2 \quad (12)$$

$$3sec\text{-}BuO_2H \longrightarrow 2\ sec\text{-}BuOH + AcEt + O_2 + H_2O \quad (33)$$

In refluxing cyclohexane or heptane, radical attack on solvent becomes more important and a variety of new competing reactions are introduced (part II[1b]). Although our data are inadequate for a full analysis, a simple conclusion emerges: the role of catalytic amounts of metal ions is largely limited to the primary processes of hydroperoxide destruction, that is, to eq 13 and 14. Since the products of decompositions differ little from those obtained from peroxide initiated decompositions (part II[1b]), metal ion–radical reactions must not compete effectively with the other reactions above at low concentrations of metal ions. This conclusion applies even to the production of *t*-butyl cyclohexyl peroxide which others[18] have proposed to arise *via* eq 34 and 35. Since the steady-state concentration of *t*-butylperoxy radicals in the system is nearly equal to that of M^{III},[19] the radical–radical combination route is equally likely and less complicated.

$$C_6H_{11}\cdot + M^{III} \longrightarrow M^{II} + C_6H_{11}^+ \quad (34)$$

$$C_6H_{11}^+ + t\text{-}BuO_2H \longrightarrow C_6H_{11}O_2t\text{-}Bu + H^+ \quad (35)$$

The relative rates of decomposition of the different hydroperoxides in alkanes are not readily explained. In *n*-pentane (as in chlorobenzene) they are in reasonable agreement with the chain lengths for radical-induced decomposition, but this difference between tertiaries and nontertiaries persists in refluxing cyclohexane or heptane, where the radical chain contribution must be very small.

The reason for the striking difference in degree of autoretardation between tertiary and nontertiary hydroperoxides is uncertain. We tentatively suggest that formic acid, which can be produced from both *t*-BuO_2H and α-cumyl O_2H but not *n*-BuO_2H or *sec*-BuO_2H, is generated in sufficient quantity to precipitate the catalyst as insoluble cobalt formate.

Decompositions in Alcohol–Chlorobenzene Mixtures. —Decompositions of *t*-BuO_2H by $CoOct_2$ in 2:3 alcohol–PhCl mixtures were severely autoretarded by deactivation and precipitation of the catalyst. 0.001 *M* $CoOct_2$ was necessary for complete decomposition (98% in 24 hr) of 0.1 *M* hydroperoxide. Initial rates (to the accuracy measurable) were only $^1/_{100}$th as fast as in pure chlorobenzene[20] and yields of acetone were much greater (Tables VI and VII). Decompositions of *sec*-BuO_2H showed little autoretardation and products (Table VI) differed little from reactions in chlorobenzene.

For *t*-BuO_2H, the effects of large amounts of *t*-BuOH on rates and products are similar to those found in free radical-induced decompositions (part II[1b]) and must be partly due to the same factor, the enhanced rate of cleavage of *t*-butoxy radicals. However, the observed difference in initial rates is much greater than can be explained by inhibition of the radical-induced chain (which could account for a factor of 8–10 at most). It suggests that alcohol affects the rate of metal ion–hydroperoxide reactions, possibly by competing for ligand sites in the metal ion complex.

TABLE VI

DECOMPOSITIONS OF 0.1 *M* BuO_2H BY 2 m*M* $CoOct_2$ IN 2:3 ALCOHOL–CHLOROBENZENE MIXTURES AT 25°

BuO_2H	Solvent	$[k_1]_0 \times 10^4$,[a] sec^{-1}	Products R_2O_2[b]	ROH[b]	R=O[b]	S=O[c]
t-BuO_2H	*t*-BuOH–PhCl	2.5	5.6		8.7	
t-BuO_2H	*i*-PrOH–PhCl	1.2	0.8	~100		101
sec-BuO_2H	*i*-PrOH–PhCl	9.2		57	37	36

[a] Average pseudo-first-order rate constant calculated at 5% decomposition. [b] Dialkyl peroxide, alcohol, or ketone from hydroperoxide in % based on RO groups. [c] Ketone from solvent in % based on hydroperoxide decomposed. Totals greater than 100% reflect lack of precision in glpc analyses.

In *i*-PrOH–PhCl a nearly clean reduction of *t*-BuO_2H to *t*-BuOH obtains. Both the cleavage of *t*-$BuO\cdot$ and the interactions of 2*t*-$BuO_2\cdot$ are suppressed, possibly by the reactions in eq 36 and 37. *sec*-BuO_2H does not reduce cleanly under identical conditions, probably because interactions of 2*sec*-$BuO_2\cdot$, being much faster than those of 2*t*-$BuO_2\cdot$ (part II[1b]), compete better with other reactions.

$$t\text{-}BuO\cdot + i\text{-}PrOH \longrightarrow t\text{-}BuOH + Me_2\dot{C}OH \quad (36)$$

$$Me_2\dot{C}OH + t\text{-}BuO_2\cdot \longrightarrow t\text{-}BuO_2H + AcMe \quad (37)$$

Complex Kinetics in Metal-Catalyzed Decompositions

Table VII summarizes typical kinetic data obtained by us and others. There is a remarkable agreement on rates of reaction and on the form of the rate expressions where these are comparable. Some investigators have held our view, that metal-catalyzed decompositions are essentially free-radical-induced decompositions initiated by metal ion–hydroperoxide interactions. Others concerned with the complexity of the kinetic expressions have proposed more complex schemes.[8,10,21] We suggest instead that the complex kinetics are simply a reflection of the metal catalyst's lack of true solubility in organic solvents. Thus, Table VII shows that most of the abnormalities are in the rate dependence on metal ion;[22] reactions are first order in hydroperoxide (or nearly so) regardless of conditions. Furthermore, the reaction order in metal ion is sensitive to solvent and temperature. The latter is most vividly demonstrated by decompositions of *t*-BuO_2H by $CoOct_2$ in chlorobenzene. Richardson's[10] results at 20° agree very well with ours at 25°; yet at 0° (where his order in [Co] varies between 0.05 and 1.5 depending on the concentration of $CoOct_2$), the rate he obtains using 0.2 m*M* $CoOct_2$ is less than one-tenth of that predicted from our results at 45 and 25°. We have found a similar nonlinear temperature dependence for reactions catalyzed by CoA_2 at 45, 25, and 0°. Reactions which are first order in metal ion have over-all E_a's of 9–12 kcal. Those with higher orders have E_a's of 17–22 kcal. Thus it appears that catalysts in "solution" may exist as fairly large aggregates even at concentrations of 0.1 m*M*. Increasing

(18) M. S. Kharasch and A. Fono, *J. Org. Chem.*, **24**, 72 (1959).
(19) J. R. Thomas, *J. Amer. Chem. Soc.*, **87**, 3935 (1965).
(20) At 0.1 m*M* Co; rates in alcohol–chlorobenzene mixtures were not simply related to [Co], but were nearer second order than first.
(21) H. Berger and A. F. Bickel, *Trans. Faraday Soc.*, **57**, 1325 (1961).
(22) Radical-induced decompositions may have complex kinetics, as well, under certain conditions (part II), but never in our experience has the order in initiating species been greater than unity.

TABLE VII

RATES OF DECOMPOSITION OF 0.01–0.1 *M* HYDROPEROXIDES AND REACTION ORDERS IN METAL IONS AS FUNCTIONS OF SOLVENT AND TEMPERATURE

Ref	Temp, °C	Solvent	Catalyst	[Metal ion], m*M*	k_1,[a] sec^{-1} × 10^4	n[b]	E_a[c]	$t_{\frac{1}{2}}$[c]
			t-BuO_2H					
d	20	PhCl	$CoOct_2$	8.5	2.3	~1		
g	25	PhCl	$CoOct_2$	10	2.3	1	12	45
g	25	2:3 *t*-BuOH–PhCl	$CoOct_2$	30	0.11	>1		
h	35	1:1 HOAc–H_2O	$K_2CoEDTA$	4440	0.038[e,f]	1 + 2	19.8	50
g	38	*n*-Pentane	$CoOct_2$	9.5	11	2		
d	50	HOAc	$Co(OAc)_2$	1040	0.14	1.3	19.7	70
i	55	HOAc	$Co(OAc)_2$	1000	0.20	1.4		
			α-Cumyl O_2H					
j	25	H_2O	$FeSO_4$	4[f]	1.1	1	11.1	0
g	45	PhCl	$CoOct_2$	9	1.9	1	12[k]	
k	50	1:1 HOAc–PhCl	$CoSt_2$	100	0.14	1.5–2	22.3	60
l	101	Nonane	$CoPalm_2$[m]	100	3.2	1	9.4	67
			α-Tetralyl O_2H					
n	49.7	Tetralin	$CoOleate_2$	24	0.04	1.7	17	34
o	50	PhCl	$CoDecanoate_2$	20[p]	1.0[p]	1		
q	50	1:1 HOAc–PhH	$Co(OAc)_2$	200	0.9	2		
r	50	Xylene	$CoOct_2$	10	0.77	2	17.4	25–77

[a] k_1 = rate/[RO_2H]. [b] Order in metal ion. [c] Calcd from k_1 at t and t_2. This clearly has no precise meaning when n at $t \neq n$ at t_2 but conveniently indicates the thermal coefficient of the rate. [d] See ref 10. [e] At [*t*-BuO_2H]$_0$ = 0.11. [f] Stoichiometric decompositions. [g] This work. [h] See ref 3. [i] See ref 8. [j] J. W. Fordham and H. L. Williams, *J. Amer. Chem. Soc.*, **72**, 4465 (1950). [k] From E. A. Kuz'mina, V. A. Shushunov, and M. K. Shchennikova [*Khim. Perekisnykh Soedin. Akad. Nauk SSSR, Inst. Obshch. i Neorgan. Khim.*, 231 (1963); *Chem. Abstr.*, **60**, 14, 360 (1964)] who agree that reactions are first order in [Co] but do not give actual rates. [l] H. Hoch and H. Kropf, *J. Prakt. Chem.*, **16**, 113 (1962). [m] Cobaltous palmitate. [n] J. Tomiska, *Collect. Czech. Chem. Commun.*, **27**, 1549 (1962). [o] A. Y. Kamiya, S. Beaton, A. Lafortune, and K. U. Ingold, *Can. J. Chem.*, **41**, 2034 (1963). [p] [M] chosen arbitrarily in order to evaluate k_1 from Ingold and coworkers'[o] bimolecular rate constant, K_2 = rate/[Co][RO_2H]. [q] Reference 12; see also A. E. Woodword and R. B. Mesrobian, *J. Am. Chem. Soc.*, **75**, 6189 (1953). [r] See ref 5.

the temperature decreases the aggregate size (and increases the effective catalyst concentration), resulting in an extraordinarily large E_a. Considerable further work would be needed to provide more than this qualitative evaluation of the situation.

Registry No.—*t*-BuO_2H, 75-91-2; α-Cumyl O_2H, 80-15-9; *n*-BuO_2H, 4813-50-7; *sec*-BuO_2H, 13020-06-9.

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Homolytic Decompositions of Hydroperoxides. V.[1a-d] Thermal Decompositions

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Solutions of 0.01–0.26 *M* *t*-butyl hydroperoxide in toluene have been thermally decomposed at 100–215°. Products included *t*-butyl alcohol, acetone, methane, CO, CO_2, bibenzyl, benzaldehyde, and benzyl alcohol in yields varying with temperature and peroxide concentration. At initial concentrations below 0.02 *M*, decompositions of hydroperoxide were first order; nevertheless, even at 0.001 *M* peroxide, at least 30% of the total decomposition at 180° was induced decomposition. Acetone is a mild catalyst of thermal decomposition. The rate constant for homolytic cleavage of the O–O bond at 170–215° is about $10^{15.8}e^{-43,000/RT}$. At 100°, extraneous unexplained factors caused a thermal decomposition 20 times as fast as expected from this relation. The absence of methanol in the products excludes a previously postulated rearrangement of *t*-butylperoxy radicals at 180°. Less detailed studies in benzene, cumene, *n*-heptane, and cyclohexane showed that these decompositions are largely radical induced in the nonaromatic solvents and are mostly homolytic in aromatic ones. Some decompositions of dilute solutions of *n*-BuO_2H, *sec*-BuO_2H, and α-cumyl hydroperoxide in toluene at 170–180° gave rates two to three times as fast as those found for *t*-BuO_2H. From the products of decomposition, 21% of the *n*-BuO· and 60% of the α-cumyl-O· radicals are estimated to cleave in toluene at 182°. About 50% of the *t*-BuO· radicals cleave under these conditions. The absence of cumene in the products from decompositions of 1.4 *M* α-cumyl hydroperoxide in toluene at 125 and 139° shows that a previously proposed reaction, $PhCH_2\cdot$ + α-cumyl O_2H → cumene + $PhCH_2O_2H$, does not occur. This research probably pushes to its limits the technique of increased dilution as a means for measuring the uncomplicated homolytic decomposition of *t*-BuO_2H. There are methods for monitoring hydroperoxide concentration at much higher dilution, but they, like the iodometric method of analysis, do not distinguish between the hydroperoxide originally present and that possibly produced from the solvent. Analyses for products, on which a postulated mechanism must ultimately rest, become exceedingly tenuous at 0.001 *M* hydroperoxide.

The thermal decomposition of hydroperoxides, unlike that of dialkyl peroxides or peroxy esters, is complex. Rate constants for decomposition in solution depend strongly on concentration, on the nature of the hydroperoxide, and on the character of the solvent, even in the absence of known catalysts such as acids, bases, certain metal ions, and olefins.[2] Even for *t*-BuO_2H, the best-behaved of the class, attempts to measure rates for thermal homolysis of the O–O bond, have given activation energies well below[3] that calculated for the reaction[4]

$$RO_2H \longrightarrow RO\cdot + \cdot OH \qquad (15)$$

and have shown unexplained rate effects in the presence of oxygen[5] and of presumably innocuous solvents.[6] Probably the most serious complication is the induced decomposition, in which radicals arising from spontaneous homolysis[7] of the O–O bond or from other sources attack the hydroperoxide (see eq 2 and 3). Thus, in

$$RO\cdot(HO\cdot) + RO_2H \longrightarrow ROH\ (HOH) + RO_2\cdot \qquad (2)$$

$$2RO_2\cdot \longrightarrow 2RO\cdot + O_2 \qquad (3)$$

chlorobenzene solution at 140°,[3] or undiluted at 100°,[8] *t*-BuO_2H decomposes almost quantitatively to *t*-BuOH and oxygen. Below 100°, where the hydroperoxide is thermally stable, induced decomposition has received intensive study and is now well understood (part II[1b]).[9,10]

We reinvestigated thermal homolysis in the hope of (1) establishing some reliable rates and activation energies, (2) determining effects of solvents on these, and (3) exploring effects of structure on thermal homolysis of some structurally simple hydroperoxides and on cleavage of alkoxy radicals at elevated temperatures. Previous work showed that induced decomposition is minimized at very low initial concentrations of hydroperoxide.[11] We have extended this work to even lower initial concentrations and to a variety of solvents, paying careful attention to both rates and products of decomposition.

Experimental Section

Analyses.—Hydroperoxides were titrated iodometrically, usually by the method described in part II,[1b] which gave consistent blank titers of 0.0008 mequiv. For concentrations of RO_2H below 0.002 *M*, 1 ml of a freshly prepared saturated aqueous solution of KI was substituted for the solid NaI. Blanks were then less than 0.0001 mequiv.

Products of decomposition were analyzed by glpc on a Carbowax 20M column after reduction of any residual hydroperoxide to alcohol with Ph_3P. Gaseous products were analyzed by mass spectroscopy.

Rate Measurements.—For kinetic runs, seven to nine Pyrex ampoules (10 mm) containing 2–3 ml of a dilute solution of hydroperoxide were degassed, sealed under vacuum, and immersed in a constant temperature bath for appropriate lengths of time; then residual hydroperoxide was titrated iodometrically. For some product studies, 20 ml of hydroperoxide solution was degassed and sealed under vacuum in a 100-ml bulb provided with a break-seal. Despite the differences in available vapor space between these runs and those in ampoules, no difference in percentages of products was observed. Thus, gas phase decomposition did not contribute significantly to the reaction.

Decompositions of *t*-BuO_2H

Solvent Purity.—Even reagent or chromatograde solvents contain impurities which affect peroxide

(1) (a) Part I: R. Hiatt, T. Mill, and F. R. Mayo, *J. Org. Chem.*, **33**, 1416 (1968). Equations 1–16 appear in part I. (b) Part II: R. Hiatt, T. Mill, K. C. Irwin, and J. K. Castleman, *ibid*, **33**, 1421 (1968). Equations 17–24 appear on part II. (c) Part III: R. Hiatt, T. Mill, K. C. Irwin, and J. K. Castleman, *ibid.*, **33**, 1428 (1968). Equation 12a and b appear in part III. (d) Part IV: R. Hiatt, K. C. Irwin, and C. W. Gould, *ibid.*, **33**, 1430 (1968). Equations 25–37 appear on part IV. (e) To whom all correspondence should be addressed at Brock University, St. Catharines, Ontario, Canada.

(2) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, p 504.

(3) E. R. Bell, J. H. Raley, F. F. Rust, F. H. Seubold, and W. E. Vaughan, *Discussions Faraday Soc.*, **10**, 242 (1951).

(4) S. W. Benson, *J. Chem. Phys.*, **40**, 1007 (1964).

(5) B. K. Morse, *J. Amer. Chem. Soc.*, **79**, 3375 (1957).

(6) C. Walling and L. Heaton, *ibid.*, **87**, 38 (1965).

(7) We realize that "homolysis" is ambiguous in the sense that *all* of their reactions under discussion are homolytic (free radical) in character. By "homolysis" we mean spontaneous homolytic cleavage of the O–O bond, and "induced" refers to any other form of decomposition.

(8) N. A. Milas and D. M. Surgenor, *ibid.*, **68**, 205 (1946).

(9) R. Hiatt, J. Clipsham, and T. Visser, *Can. J. Chem.*, **42**, 2754 (1964).

(10) A. Factor, C. A. Russell, and T. G. Traylor, *J. Amer. Chem. Soc.*, **87**, 3692 (1965).

(11) R. Hiatt and W. M. J. Strachan, *J. Org. Chem.*, **28**, 1893 (1963).

TABLE I

THERMAL DECOMPOSITION OF t-BuO_2H IN AROMATIC SOLVENTS

Temp, °C	$[t\text{-}BuO_2H]_0$, mol/l.	$k_1 \times 10^5$, sec^{-1}	Yields based on RO_2H decomposed, % AcMe	t-BuOH	S—S[a]	S—OH[b]	S=O[c]
			In Toluene				
100.0	0.0161	0.0057	~1	87	31	29	46
172.5	0.0012	0.92			48		
181.5	0.025	2.69	46	47	41	26	7.3[d]
192.6	0.021	8.3	52	48	30		
204.5	0.010	15.2			45	8	<0.5
204.5	0.027	18.0	62	36	43	21	4
214.9	0.011	32.4	70	28	51	6	<0.5
			In Benzene				
172.5	0.022	4.64[e]	62	22	3		
172.3	0.022	1.09					
182.6	0.021	3.1					
			In Cumene				
182.6	0.021	8.1	50	50	50	28	5.8[f]
182.6	0.040	9.6					
182.6	0.090	14.3	36	64		47	8.3
			In Toluene with Added Material				
181.2	0.025	2.81				0.026 M t-BuOH added	
181.2	0.025	3.30				0.026 M AcMe added	
181.5	0.022	3.40			34	[g]	
181.5	0.025	4.36			37	[h]	

[a] Products from solvent were bibenzyl from toluene, biphenyl from benzene, and bicumyl from cumene. [b] Products from solvent were benzyl alcohol from toluene and α-cumyl alcohol from cumene. [c] Products from solvent were benzaldehyde from toluene and acetophenone from cumene. [d] Also 32% CH_4, 0.5% CO, 0.04% CO_2, 41% H_2O, *no* O_2. [e] Solvent not treated with CaH_2. [f] Also 13% α-methylstyrene. [g] Fresh t-BuO_2H added to a decomposed mixture of 0.25 M t-BuO_2H in toluene. [h] Ampoules packed with broken Pyrex tubing to increase surface area sevenfold.

decomposition. Walling and Heaton[6] found excessively rapid decomposition of t-BuO_2H in chlorinated aromatic hydrocarbons. We found that aliphatic hydrocarbons were particularly bad, the half-life of t-BuO_2H in n-heptane at 100° being less than 3 hr. Fractional distillation with or without thermal decomposition of 2,2′-azobis(2-methylpropionitrile) (ABN) in the solvent was ineffective. By accident it was discovered that refluxing the solvent over CaH_2 before distillation removed the catalytic agent, although the solvent composition as determined by glpc was unchanged. With this treatment the half-life of t-BuO_2H in n-heptane at 100° was about 1000 hr. In benzene at 180° the half-life was increased fourfold. The saturation of solvents with water had no deleterious effect. Without understanding the results of this treatment, we are convinced of its efficacy.[12]

Thermal Decomposition of t-BuO_2H in Aromatic Solvents. Results.—Table I shows the rates and products of the thermal decomposition of t-BuO_2H in toluene, benzene, and cumene at 100–215°. At 170 and 180°, rates of decomposition were first order in hydroperoxide to at least 90% decomposition; they were the same in benzene and toluene and slightly higher in cumene.

A plot of first-order rate constants and products at 180° as a function of $[t\text{-}BuO_2H]_0$ (Figure 1) clearly shows a change in mechanism of decomposition at 0.02–0.03 M. The relative insensitivity of k_{15} to $[t\text{-}BuO_2H]_0$ below this concentration suggests that here the reaction is largely a true homolysis.[13] The rate constants are about half as large as previously reported rates[11] in benzene at 180°. An Arrhenius plot for runs at 170–190° gives an E_a of 43 ± 1 kcal/mol, in good agreement with the value calculated by Benson.[4] The A factor, $10^{16.1}$, is reasonable for a first-order reaction.

Results above and below this optimum temperature range were less conclusive. In toluene at 100° the rate, measured over 3 months (about one half-life), was cleanly first order, but k_1 was 20 times that extrapolated from the decompositions at 170–190°. At 190–215° first-order rate constants were more sensitive to initial concentration (Table I). Also, plots of log $[RO_2H]$ *vs.* time became slightly curved after one half-life. For 0.01 M t-BuO_2H in toluene at 205–215° (from k_1 for the first half-life), E_a was only 34.5 kcal/mol.

Closer scrutiny of the 180° reaction brought out some complications. First, there appeared to be some decomposition on the Pyrex walls. Increasing the surface to volume ratio sevenfold by filling the ampoules with crushed Pyrex tubing increased the first-order rate constant by 60% (Table I). A very small amount of added acetone in 0.02 M t-BuO_2H in toluene increased k_{15} significantly (Table I). Decomposing 0.02 M t-BuO_2H in the total reacted solution from a previous run caused a similar increase[14] in k_{15}. Thus, decompo-

(12) Possible catalysts include trace amounts of thiols, acids, and metal ions. Since extraction of benzene with aqueous NaOH before use was about half as effective as treatment with CaH_2, acids or thiols are good possibilities. Autocatalysis in the thermal decomposition of silyl peroxides in chlorobenzene results from generation of HCl by reaction of radicals with the solvent: R. Hiatt, *Can. J. Chem.*, **42**, 985 (1964).

(13) Added 0.003 M t-Bu_2O_2 to 0.025 M t-BuO_2H in benzene at 170° decomposed an average of only 1.2 molecules of hydroperoxide per molecule of dialkyl peroxide decomposed, a chain length of 0.6.

(14) Addition of small amounts of t-BuOH did not affect the thermal decomposition. Attempts to decompose 0.02 M t-BuO_2H in t-BuOH as solvent resulted in explosion of the ampoule minutes after it was put in an 180° oil bath. An ampoule of 0.02 M t-BuO_2H in 20% t-BuOH-80% benzene exploded after 2 hr in a 170° bath.

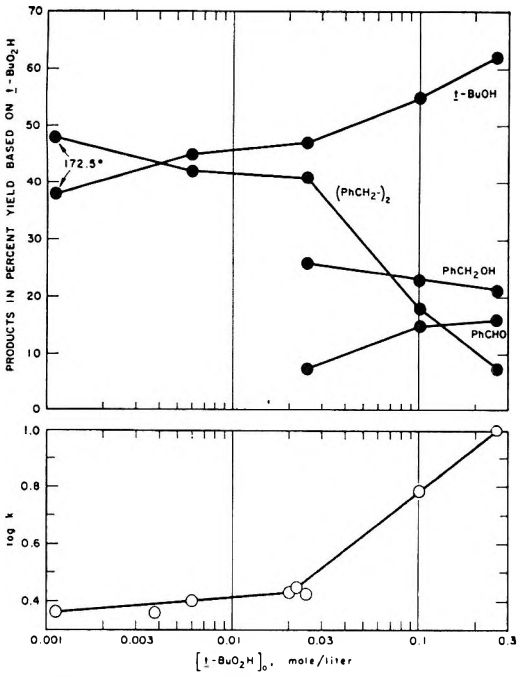


Figure 1.—Rate constants and products of decomposition of t-BuO_2H in toluene at 182°.

sitions at 180° (at least at 0.02 M) are slightly autocatalytic, and the straight line plots of log $[RO_2H]$ *vs.* time result from a compensatory effect of autocatalysis and decomposition greater than first order.

Discussion.—Our analysis of these complex results (assuming that they are valid)[15] is based on the products, how these change with $[t\text{-}BuO_2H]_0$, and how they compare with products of t-Bu_2O_2 decomposed in similar circumstances (Table II). The argument is based mostly on the results in toluene, since these are the most comprehensive, but findings in other solvents are used where appropriate. The results below suggest the following. (1) At 180° for $[t\text{-}BuO_2H]_0 > 0.03$ M, decomposition proceeds mainly by a t-BuO·-induced reaction of the usual type. (2) At 180° for $[t\text{-}BuO_2H]_0 \geq 0.025$ M, homolysis accounts for 40–70%

TABLE II

PRODUCTS OF THERMAL DECOMPOSITION OF t-Bu_2O_2 IN TOLUENE[a]

Temp, °C	$[t\text{-}Bu_2O_2]_0$, mol/l.	Yields based on t-Bu_2O_2 decomposed, % Acetone	t-BuOH	$(PhCH_2)_2$
100	0.294			100
171.5	0.0244	52	47	80
181.5	0.0348	58	39	67
181.5[a]	0.0373	57	39	60

[a] All runs were carried to more than eight half-lives except the first, for which decomposition was 18% in 71 hr. The ampoules in the last run were filled with crushed Pyrex tubing.

of the reaction, so that the true k_1 at 182.6° is approximately 1×10^{-5} sec^{-1}. The rest of the reaction is mainly short chain induced decomposition involving benzyl radical attack on the *oxygen* of t-BuO_2H. (3) At 215°, for $[t\text{-}BuO_2H]_0 = 0.01$ M, decomposition is nearly all by spontaneous homolysis. (4) The reaction at 100° is partly induced but at least 30% is a bimolecular homolysis in which hydroperoxide reacts with the walls, with solvent, with itself, or with some other species to produce radicals.

Decompositions at 180°.—Above 0.02 M, increases in $[t\text{-}BuO_2H]_0$ result in lower yields of bibenzyl and higher $[t\text{-BuOH}]/[\text{acetone}]$ ratios (Figure 1). The higher concentration of t-BuO_2H thus favors t-BuO· + t-$BuO_2H \rightarrow t$-BuO_2· + t-BuOH (eq 2) over other fates for the t-butoxy radical. Decomposition probably occurs largely by an induced chain of the usual type, O_2 being produced by interaction of $2t$-BuO_2· radicals and scavenged by benzyl (or methyl) radicals. (Yields of benzaldehyde should be a good index to this kind of reaction.) Chain lengths must be at least 4–5, since decomposition[4] is $^3/_2$ (or $^4/_3$) order in $[t\text{-}BuO_2H]$.

At $[t\text{-}BuO_2H]_0 \leq 0.02$ M, most t-BuO· radicals abstract from toluene or cleave, since t-BuOH/acetone ratios are relatively insensitive to $[t\text{-}BuO_2H]_0$ (Figure 1) and are in good agreement with those from t-Bu_2O_2 decompositions (Table II). Thus the relevant competition at these concentrations of t-BuO_2H is

$$PhCH_2\cdot + t\text{-}BuO_2H \rightarrow \text{(induced decomposition)} \quad (38)$$

$$PhCH_2\cdot + PhCH_2\cdot \rightarrow \text{bibenzyl (termination)} \quad (39)$$

The substantial yields of bibenzyl show that a large fraction of the hydroperoxide decomposes *via* homolysis. The questions are (1) how much, if any, disappears by a benzyl radical-induced decomposition, and (2) what is its mechanism. The discussion below shows that there is no simple answer for either question.

If *all* hydroxyl radicals (which can only be formed by homolysis) abstract hydrogen, then the yield of water (41% at $[t\text{-}BuO_2H]_0 = 0.02$ M, Table I) is identical with the amount of homolysis. This supposition seems sound in view of the activity of ·OH, the availability of the solvent, and the low steady-state concentration of other radicals with which it might couple, but the actual yield of H_2O is subject to considerable experimental uncertainty.

A better criterion for homolysis is the yield of identifiable products of radical–radical termination. For $[t\text{-}BuO_2H]_0 \leq 0.2$ M we could find only about 50% [40–45% $(PhCH_2)_2$ and 7% PhCHO[17]].[18] This would be acceptable evidence for 50% homolysis except for the results of the t-Bu_2O_2 pyrolyses. At 180° in toluene this presumably well-behaved material gave only 60–70% of identifiable radical termination products (all bibenzyl). We do not understand why the yield of bibenzyl from t-Bu_2O_2 decreased with increasing temperature (Table II) but are reluctant to ascribe the decrease to induced decomposition. Possibly it is due to some as yet un-

(15) Possibly surface catalysis is responsible for the faster than expected results at 100°. The experiments with packed vessels indicate that surface effects, though present, are small at 180°. The slower than expected rates above 200° could mean simply that temperatures in the reaction vessels did not attain bath temperature during the relatively short reaction times. However, the log plots for individual runs showed no evidence of any 'warm up" period. Moreover, the rate constants for decompositions of α-cumyl hydroperoxide[16] in cumene or in benzene show the same S-shaped Arrhenius plot at somewhat lower temperatures.

(16) G. H. Twigg, G. W. Godin, H. C. Bailey, and J. Holden, *Erdoel Kohle*, **15**, 74 (1962).

(17) Though PhCHO is a product of induced decomposition, it must also be a product of a termination reaction between $PhCH_2O$· and some other radical (X·), *e.g.*, $PhCH_2O\cdot - X\cdot \rightarrow XH + PhCHO$.

(18) Other possible termination products looked for *but not found* included ethane, ethylbenzene, xylenes, t-$BuOCH_3$, CH_3OH, and tarry residues. We could not be sure about the absence of other t-butyl ethers, but, since ~97% of t-BuO groups was accounted for in other products, their yield could not be significant. It seems most unlikely that any of the benzyl alcohol results from coupling of ·OH and $PhCH_2$·.

discovered products of $CH_3\cdot$ radicals; the yield of these parallels the termination-products gap, and our material balance for them was not good.

Since t-BuO_2H can give only half as many methyl radicals as t-Bu_2O_2, we might accept 15–20% as the amount of undiscovered termination products, thus setting 30% as the lower limit for induced decomposition of the hydroperoxide.

The mechanism of the induced decomposition depends on whether benzyl radicals abstract *hydrogen* from t-BuO_2H as Benson[4] asserted, or attack at oxygen to form benzyl alcohol directly, as Twigg, *et al.*,[16] suggested.[19] The yield of $PhCH_2OH$, though curiously insensitive to $[t\text{-}BuO_2H]_0$ (Figure 1), is less informative than the yield of α-cumyl alcohol (or the α-cumyl alcohol/acetophenone ratio) when t-BuO_2H is decomposed in cumene[20] (Table I). Cleavage of cumyloxy radicals to acetophenone and methyl is known to proceed more readily than the cleavage of t-$BuO\cdot$;[21] yet, while yields of acetone and t-BuOH were about equal, five to six *times as much cumyl alcohol* as acetophenone was formed. Thus the bulk of the cumyl alcohol cannot be formed from cumyloxy radicals.

Translated to the results in toluene, this suggests that, while *some* of the benzyl alcohol is undoubtedly formed from benzyloxy radicals (since some benzaldehyde is also produced), *most* of it is not. The alternatives are that it is formed by coupling of benzyl and hydroxyl (which has already been ruled out) or that it is formed directly by attack of benzyl$\cdot$ on t-BuO_2H (eq 40).

$$PhCH_2\cdot + t\text{-}BuO_2H \longrightarrow PhCH_2OH + t\text{-}BuO\cdot \quad (40)$$

In accepting the reaction in eq 40 as the mechanism, we are not suggesting that the benzyl radical is unable to abstract hydrogen from t-BuO_2H. Most probably it *does*, but owing to the low steady-state concentrations of radicals, the reverse reaction (eq 41) occurs more

$$t\text{-}BuO_2\cdot + PhCH_3 \longrightarrow t\text{-}BuO_2H + PhCH_2\cdot \quad (41)$$

frequently than any other reactions of t-$BuO_2\cdot$ radicals, leading to an induced chain.[22]

The rate expression for the induced part of the decomposition, according to the proposed mechanism in eq 42 is $^3/_2$ order in hydroperoxide, but, since the induced reaction accounts for less than half of the decomposition, the observed deviation from first-order kinetics is small.

$$-d[t\text{-}BuO_2H]/dt = k_{15}[t\text{-}BuO_2H] + k_{16}(k_{15}/k_3)^{1/2}[t\text{-}BuO_2H]^{3/2} \quad (42)$$

Decompositions at 205–215° and at 100°.—The low yields of oxidized solvent show that induced decomposition was minimal at 205–215° when $[t\text{-}BuO_2H]_0 = 0.01\ M$. At 215° the yield of bibenzyl was only 51%, but by extrapolation from Table II, bibenzyl yields expected from t-Bu_2O_2 would be no higher. An assumed E_a of 43 kcal and a k_1 at 180° of 1×10^{-5} sec^{-1} gives 31×10^{-5} sec^{-1} for k_1 at 215°, in excellent agreement with the experimental value.

At 100° the rate (much faster than predicted) and the high yields of benzaldehyde and benzyl alcohol imply an induced decomposition. However, there is a 31% yield of bibenzyl. Less than $^1/_{20}$th of this can arise from unimolecular homolysis if the Arrhenius parameters obtained at higher temperatures are correct. Instead it must come from an externally assisted homolysis, perhaps catalyzed by the walls. The results on surface effects at 180° (Table VI) show that a wall-catalyzed reaction can yield almost as much bibenzyl as the unimolecular homolysis. However, low temperature homolyses of hydroperoxides are too confused and complex to allow any definite answers at this time. Hydroperoxides may react bimolecularly with another hydroperoxide,[23–25] with a ketone,[26,27] with an olefin,[6,28] perhaps even with solvent,[16,29] to produce radicals. Our own results are paradoxical if the formation of *benzaldehyde* as well as of bibenzyl is counted as chain termination. Further work is indicated.

Rearrangements of Peroxy Radicals.—The rearrangement of t-$BuO_2\cdot$ has been proposed to explain the formation of CH_3OH and acetone in gas phase oxidations of isobutylene,[30] rather than the alternate

$$t\text{-}BuO_2\cdot \longrightarrow CH_3{-}\overset{CH_3}{\overset{|}{C}}{-}O{-}O{-}CH_3 \longrightarrow \text{acetone} + CH_3O\cdot$$

interaction of $2t$-$BuO_2\cdot$ radicals to give $2t$-$BuO\cdot$ radicals (which cleave to $CH_3\cdot$ and acetone) and O_2. The absence of methanol in the products of our decompositions shows that this rearrangement does not occur in solution at 180°. However, this may not be significant, since in the gas phase concentration factors favor intramolecular reactions over their intermolecular alternatives.[31]

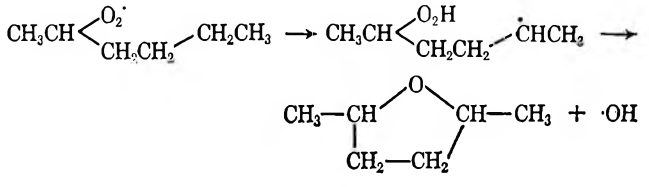
Decompositions of t-BuO_2H in Aliphatic Hydrocarbons.—Thermal decompositions of 0.01–0.02 M t-BuO_2H in cyclohexane and in n-heptane at 170° gave substantially the same first-order rate constants as reported by Bell, *et al.*[3] (Table III). Even at those low concentrations, rate constants were dependent on

(19) The work of W. A. Pryor, A. Lee, and C. E. Witt [*J. Amer. Chem. Soc.*, **86**, 4229 (1964)] suggests that below 100° radical displacements on O–O bonds are infrequent. However, at 170–190° the situation appears to be different.

(20) This argument assumes that mechanisms in cumene and toluene are similar, as is indicated by our results and those of Twigg and coworkers.[16]

(21) See ref 2, pp 503–505. To make sure of this point, we decomposed 0.02 M α-cumyl hydroperoxide in toluene at 182° and found 1.6 times as much acetophenone as α-cumyl alcohol in the products (see below).

(22) The formation of heterocycles in the gas phase oxidation of hexane [C. F. Cullis, A. Fisk, A. Saeed, D. L. Trimm, *Proc. Roy. Soc.* **A289**, 402 (1966)] at 275° is analogous. Reabstraction of H$\cdot$ undoubtedly occurs, but the only reaction to effect an irreversible change is the radical displacement on oxygen.



(23) D. E. Van Sickle, F. R. Mayo, and R. M. Arluck, *J. Amer. Chem. Soc.*, **87**, 4832 (1965).

(24) J. L. Bolland, *Trans. Faraday Soc.*, **46**, 358 (1950).

(25) E. T. Denisov, *Fiz. Khim.*, **38**, 2085 (1964).

(26) E. T. Denisov, V. V. Kharatonov, and E. N. Raspupova, *Kinet. Katal.*, **5**, 981 (1964); *Chem. Abstr.*, **62**, 11657 (1965).

(27) Von K. Uberreiter and W. Rabel, *Makromol. Chem.*, **68**, 12 (1963).

(28) E. T. Denisov and L. N. Denisova, *Dokl. Akad. Nauk SSSR*, **157**, 907 (1964).

(29) V. L. Antonovskii, E. T. Denisov, and L. V. Solntseva, *Kinet. Katal.*, **6**, 815 (1965); *Chem. Abstr.*, **64**, 1923 (1966).

(30) (a) V. Ya. Shtern, "The Gas-Phase Oxidation and Hydrocarbons," translated by M. F. Mullins, The Macmillan Co., New York, N. Y., 1964, p 463–466. (b) A. P. Zeelenberg and A. F. Bickel, *J. Chem. Soc.*, 4014 (1961).

(31) A. Fish, *Quart. Rev.*, **18**, 243 (1964).

TABLE III

DECOMPOSITION OF *t*-BuO_2H IN ALIPHATIC HYDROCARBONS

Solvent	Temp, °C	$[t\text{-}BuO_2H]_0$, mol/l.	$k_i \times 10^5$, sec^{-1}	Yields based on RO_2H decomposed, % AcMe	*t*-BuOH	S—S[a]	S—OH[b]	S=O[c]
Cyclohexane	100.0	0.021	0.012	1.5[d]	80	0	59	9
	172.0	0.010	10.8					
	172.0	0.025	9.6					
	182	0.019		Some[d]	85	0	66	3.3
	172.0	0.024	7.3					
n-Heptane	172.0	0.022	4.3[e]					
	172.0	0.046	14.1					
Octane	169.0	0.05	7.0[f]					

[a] The product from solvent was bicyclohexyl. [b] The product from solvent was cyclohexanol. [c] The product from solvent was cyclohexanone. [d] Acetone largely obscured by cyclohexane on glpc; quantitative estimation not attempted. [e] With 0.0037 *M* *t*-Bu_2O_2 added; initial rate from part II.[1b] [f] Taken from Bell, *et al.*[3]

TABLE IV

DECOMPOSITIONS OF α-CUMYL O_2H, *n*-BuO_2H, AND *sec*-BuO_2H IN TOLUENE

Temp, °C	$[RO_2H]_0$, mol/l.	$k_1 \times 10^5$, sec^{-1}	Yields based on RO_2H decomposed, % R=O[a]	ROH[b]	PhCHO	$PhCH_2OH$	$(PhCH_2)_2$
			α-Cumyl O_2H				
182.3	0.0214	6.45	51	32	5.2	21	17
139	1.4	3[c]	28	65	7.6	7.1	0[c]
125	1.0	0.9[c]	25	56	5.6	11	0[c]
			n-BuO_2H				
172.0	0.0116	2.2[d]					
172.0	0.0300	4.2[d]					
172.0	0.0638	6.4[d]					
182.3	0.0060	3.2[d]					
182.3	0.0112	4.8[d]	16	63[e]	3	9	30
182.3	0.0193		16	62			
			sec-BuO_2H				
172.0	0.027	2.65					
182.3	0.0127	4.9	12	20			40
182.3	0.0186		22	33[f]			

[a] Ketone or aldehyde[a] from hydroperoxide radical. [b] Alcohol from hydroperoxide radical. [c] Estimated from times for 90% decomposition. [d] $(-2[RO_2H]/dt)_0/[RO_2H]_0$. [e] No carboxylic acid. [f] Also 19% CH_3CHO.

$[t\text{-}BuO_2H]_0$ and their 10–15-fold increase over those in benzene or toluene suggests strongly that homolytic decomposition accounts for little of the hydroperoxide disappearance. No oxygen or other gas was produced, but large quantities of oxygenated solvent molecules were found. Decomposition in cyclohexane gave cyclohexanone and cyclohexanol, but *no* bicyclohexyl. Cyclohexene may have been produced in *small* quantities,[32] but was not a major product.

In radical-induced decompositions of *t*-BuO_2H, (part II[1b]), we found that small amounts of *t*-Bu_2O_2 had a pronounced effect (Table III). In contrast to the effect of added *t*-Bu_2O_2 in benzene, the rate enhancement was large and persisted long after most of the *t*-Bu_2O_2 should have decomposed.

The prevalence of complexing between hydroperoxides and aromatic solvents has recently been documented.[33] We have expected to ascertain what effect this would have on the rate of homolytic cleavage of the O–O bond by comparing thermal rates in toluene with those in nonaromatic hydrocarbons. However, because of the complexity of the thermal decomposition in alkanes at 170–180° it is unlikely that a homolytic rate can be measured under these conditions. The controlling factor appears to be formation of thermally unstable peroxides which decompose to give degenerate chain branching (part II[1b]). At 100° these

$$t\text{-}BuO_2\cdot + S\cdot \longrightarrow t\text{-}BuO_2S \longrightarrow t\text{-}BuO\cdot + SO\cdot \quad (43)$$

peroxides are relatively stable and contribute little to radical-induced decomposition.

Decomposition of α-Cumyl Hydroperoxide in Toluene

The results of decomposition of 0.02 *M* α-cumyl hydroperoxide in toluene at 182° (Table IV) were needed to substantiate the conclusions of the preceding section. The decompositions at high concentrations and low temperatures were done in order to investigate claims by Shushunov and coworkers,[34] who postulated the reaction in eq 44 because they re-

$$PhCMe_2{}^*\cdot + PhCMe_2O_2H \longrightarrow PhCMe_2{}^*O_2H + PhCMe_2\cdot \quad (44)$$

covered ^{14}C-labeled cumene from decomposition of ^{14}C-labeled α-cumyl hydroperoxide in unlabeled cumene. We reasoned that decomposition of the same concentration of α-cumyl O_2H in toluene should yield cumene if such a mechanism were operative. We found *no* cumene on the most scrupulous examination of the products. Examination of these authors'

(32) We were unable to effect a practicable glpc separation of trace amounts of cyclohexene from cyclohexane. As little as 0.1% bicyclohexyl could have been observed. We have found bicyclohexyl when other free radical initiators have been decomposed in cyclohexane, but never when *t*-BuO_2H has also been present in the solution (part II[1b]).

(33) C. Walling and L. Heaton, *J. Amer. Chem. Soc.*, **87**, 38 (1965).

(34) M. R. Leonov, B. A. Redoshkin, and V. A. Shushunov, *Zh. Obhsch. Khim.*, **32**, 3959 (1962).

experimental techniques convinces us that they were misled by incomplete separation of decomposition products from the solvent.

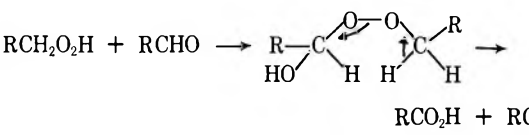
Decompositions of *n*-BuO_2H and *sec*-BuO_2H in Toluene at 170–180°

Thermal decompositions of dilute solutions of *n*-BuO_2H and *sec*-BuO_2H in toluene were carried out to determine the extent of homolysis and to gain some information on cleavage reactions of primary and secondary alkoxy radicals under these conditions. Although both hydroperoxides were slightly contaminated with their parent alcohols, this was not expected to invalidate the results. Rate constants and products are shown in Table IV.

Decompositions of *n*-BuO_2H were autocatalytic, even at 0.01 *M* in toluene. Plots of per cent of RO_2H *vs.* time were linear, and the first-order rate constants in Table IV are calculated from the initial rates of hydroperoxide decomposition determined from such plots. Values of k_1 so determined were approximately proportional to $[n\text{-}BuO_2H]^{1/2}$ and suggested induced decomposition, although the rates of lowest initial concentration and the yields of bibenzyl were not much different from those for *t*-BuO_2H under similar circumstances.

Autocatalysis for *n*-BuO_2H was not surprising in view of the Mosher[35] reaction for primary hydroperoxides, but the absence of butyric acid in the products

(35) H. S. Mosher and L. J. Durham *J. Amer. Chem. Soc.* **82**, 4537 (1960).



$$RCH_2O_2H + RCHO \longrightarrow \text{(intermediate)} \longrightarrow RCO_2H + RCHO + H_2$$

appeared to eliminate any large contribution from this reaction. The evolved gases were not analyzed.

sec-BuO_2H gave reasonably good first-order plots for decomposition and gave as much or more bibenzyl as *n*-BuO_2H did.

In product studies on completely decomposed solutions, only 79% of *n*-BuO residues and 74% of *sec*-BuO residues from the respective hydroperoxides were accounted for. Up to 21% *n*-BuO· radicals could have been lost through cleavage to Pr· + CH_2O··. *sec*-BuO· radicals can cleave in two ways. While the production of methane in the thermal decomposition of *sec*-Bu_2O_2 in toluene at 100° (part II[1b]) suggests that at 180° CH_3· radicals and EtCHO are being formed, we were unable to find the expected propionaldehyde or carboxylic acids in the products. Thus, there appear to be many opportunities for further experimental work on thermal decomposition of primary and secondary hydroperoxides, but little possibility of obtaining clean reactions and high yields of single products.

Registry No.—*t*-BuO_2H, 75-91-2; *t*-Bu_2O_2, 110-05-4; α-cumyl O_2H, 80-15-9; *n*-BuO_2H, 4813-50-7; *s*-BuO_2H, 13020-06-9.

Acknowledgment.—Mr. Brian Guilbert assisted with part of the experimental work.

Strained Organic Molecules. I. 1,5,6-Triphenyltricyclo[3.1.0.0^{2,6}]hexan-3-one[1-3]

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Received July 11, 1967

The synthesis of 1,5,6-triphenyltricyclo[3.1.0.0^{2,6}]hexan-3-one (I) from 1-(1,2,3-triphenylcycloprop-2-enyl)-3-diazopropan-2-one (II) is described. Upon heating I rearranges quantitatively to 3,4,5-triphenylphenol. In base, I readily gives 4,5,6-triphenylbicyclo[3.1.0]hex-3-en-2-one (IV). Upon irradiation with ultraviolet light I rearranges almost exclusively to 2,4,5-triphenylphenol, whereas IV gives substantial amounts of both 3,4,5-triphenylphenol and 2,4,5-triphenylphenol. Compound I reacts with methylmagnesium iodide to give 3-methyl-1,5,6-triphenyltricyclo[3.1.0.0^{2,6}]-3-hexanol (V).

Since 1961 the intramolecular cyclization of "carbenes"[4] has been used to synthesize a number of strained ring compounds. We wish to report on such a synthesis of 1,5,6-triphenyltricyclo[3.1.0.0^{2,6}]hexan-3-one (I) and some of its reactions. Masamune and coworkers[5] have communicated the results of extensive studies on an analogous compound, 1,6-diphenyltricyclo[3.1.0.0^{2,6}]hexan-3-one, and the next lower homolog, 1,5-diphenyltricyclo[2.1.0.0^{2,5}]pentan-3-one.

Compound II, (1,2,3-triphenylcycloprop-2-enyl)acetic acid, was prepared in good yield by the hydrolysis of the crude reaction product from treatment of triphenylcyclopropenyl bromide with ethyl bromoacetate in the presence of zinc in refluxing benzene–ether. It had the typical uv spectrum of a diphenylcyclopropene double bond[6] and the infrared spectrum and analysis also supported the proposed structure (see Experimental Section).

Compound III, 1-(1,2,3-triphenylcycloprop-2-enyl)-3-diazopropan-2-one, was synthesized from the acid chloride of II and diazomethane in the usual manner. Its spectra and analysis supported its structure. When this diazo ketone was treated with copper in refluxing benzene, a good yield of compound I was obtained after chromatography. The structure of I was indicated by analysis and by spectral and chemical properties. The infrared spectrum showed a carbonyl

(1) Preliminary communications of this work have been published: A. Small, *J. Amer. Chem. Soc.*, **86**, 2091 (1964); A. M. Small, *Chem. Commun.*, 243 (1965).

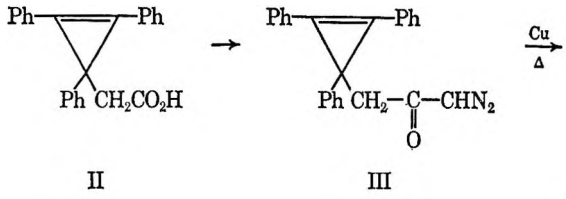
(2) This compound was previously named 4,5,6-triphenyltricyclo-[2.1.1.0^{5,6}]hexan-2-one but renamed to follow the IUPAC rules as pointed out by Meinwald.[3]

(3) J. Meinwald and J. K. Crandall, *J. Amer. Chem. Soc.*, **88**, 1292 (1966).

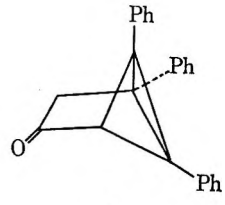
(4) The first example of such a cyclization was reported by G. Stork and J. Ficini, *ibid.*, **83**, 4678 (1961).

(5) (a) S. Masamune, *ibid.*, **86**, 735 (1964); (b) S. Masamune, *Tetrahedron Lett.*, 945 (1965); (c) S. Masamune and N. T. Castellucci, *Proc. Chem. Soc.*, 298 (1964). (d) S. Masamune, *et al.*, *Tetrahedron Lett.*, 193 (1966).

(6) R. Breslow and C. Yuan, *J. Amer. Chem. Soc.*, **80**, 5991 (1958), and subsequent papers by R. Breslow and coworkers.



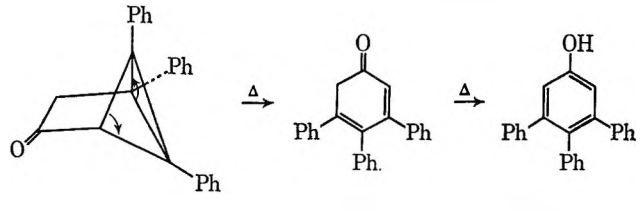
II III



I

band at 1750 cm^{-1} typical of a five-membered ring ketone.[7] The ultraviolet spectrum showed a shoulder at 243 mμ (log ε 4.23). Thus, this compound shows a strong chromophore, typical of other diphenylbicyclobutyl derivatives.[8] The intensity of the ultraviolet absorption is not surprising in view of the large amount of π character in the 1–3-carbon bridge of bicyclobutanes.[9] The nmr spectrum and analysis also agreed with the proposed structure, showing only a 15-proton multiplet centered at 7.2 for the phenyl hydrogens, a one-proton singlet at 3.2 for the bridgehead hydrogen, and a two-proton singlet at 2.6 ppm for the methylene hydrogens. In comparison 1,6-diphenyltricyclo[3.1.0.$0^{2,6}$]hexan-3-one has the following chemical shift values: phenyl, 7.1; bridgehead hydrogens, 3.4 and 3.2; methylene hydrogens, 2.0 ppm.[5b] Since Silverstein and Bassler[10] indicate a chemical-shift change of 0.35 ppm for adding a phenyl β to a methylene group, the nmr spectra of the two tricyclic compounds agree rather closely.

Further evidence for the structure of compound I are the following reactions. Upon melting or heating briefly at 180° this compound rearranges quantitatively to 3,4,5-triphenylphenol, identified by comparison with an authentic sample. The rearrangement simply involves a bond reorganization to the keto form of the phenol which then tautomerizes. This



reaction could have been predicted from the facility and mechanism of the thermal rearrangement of bicyclobutane and simple derivatives.[9,11] Stabilization by the phenyl substituents of the transition state for this reaction should also enhance the reactivity. Ma-

(7) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 42.

(8) For example, 1,5-diphenyltricyclo[2.1.0.$0^{2,5}$]pentan-3-one showed λ_{max} 242 mμ (log ε 4.16),[5a] 1,6-diphenyltricyclo[3.1.0.$0^{2,6}$]hexan-3-one showed λ_{max} 255 mμ (log ε 4.08),[5b] and methyl 1,3-diphenylbicyclobutane-2-carboxylate showed λ_{max} 270 mμ (log ε 3.95).[5b]

(9) See M. Pomerantz and E. W. Abrahamson, *J. Amer. Chem. Soc.*, **88**, 3970 (1966), and references cited therein.

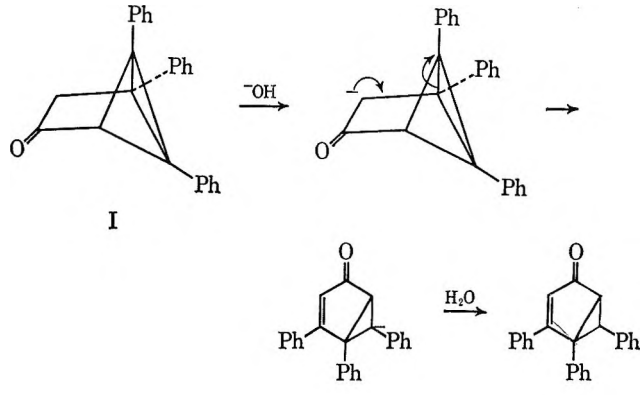
(10) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 1st ed, John Wiley and Sons, Inc., New York, N. Y., 1962, p 83.

(11) See K. B. Wiberg and J. M. Lavanish, *J. Amer. Chem. Soc.*, **88**, 5272 (1966), and references cited therein.

samune[5c] has also observed the facile thermal isomerization of 1,6-diphenyltricyclo[3.1.0.$0^{2,6}$]hexan-3-one to 3,4-diphenylphenol.

In the presence of base the tricyclic ketone rearranges readily to 4,5,6-triphenylbicyclo[3.1.0]hex-3-en-2-one. (IV). This reaction can take place by the mechanism shown in Scheme I. The driving force for the reaction is relief of strain and formation of the phenyl and carbonyl conjugated double bond.

SCHEME I



IV

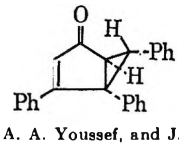
The structure of IV was ascertained from its spectral and photochemical properties. Its carbonyl band at 1690 cm^{-1} in the infrared and its λ_{max} 281 mμ (log ε 4.14) in the ultraviolet are in the region expected for a 3-phenylcyclopent-2-en-1-one.[12] The nmr spectrum also agreed with the structure (see Experimental Section). The low value (J = 4 cps) of the coupling constant between the cyclopropyl protons suggests that these two hydrogens are *trans*.[13] This would mean that in the ring opening of compound I, the cyclopropyl anion is protonated before it has a chance to epimerize.[14] This is not surprising in view of the high exchange *vs.* racemization rate of cyanocyclopropanes[15] and the stereospecific opening in base of 1,5-diphenyltricyclo[2.1.0.$0^{2,5}$]pentan-3-one to a bicyclobutyl derivative.[5b]

Ultraviolet irradiation of compound IV in a Pyrex vessel gave a small amount of acidic material which was not characterized, a 50% yield of crude 2,4,5-triphenylphenol, and a 20% yield of crude 3,4,5-triphenylphenol. Both products were characterized by comparison with samples prepared by a different route. This photochemical behavior is readily explained on the basis of the mechanism proposed by Zimmerman for the rearrangement of 6,6-diphenylbicyclo[3.1.0]-hex-3-en-2-one and related compounds.[16] The photo-

(12) See examples in C. F. H. Allen and J. A. VanAllen, *ibid.*, **77**, 2315 (1955); P. Yates, N. Yoda, W. Brown, and B. Mann, *ibid.*, **80**, 202 (1958); B. Eistert and A. Langbein, *Ann.*, **678**, 78 (1964).

(13) J. D. Graham and M. T. Rogers, *J. Amer. Chem. Soc.*, **84**, 2249 (1962).

(14) These considerations lead to the tentative formulation of the stereochemistry of IV as



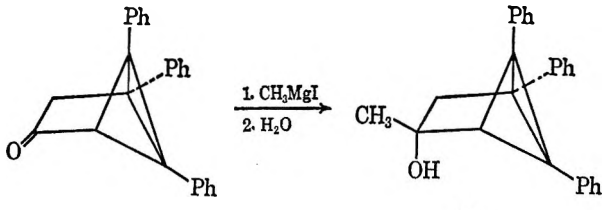
(15) H. M. Walborsky, A. A. Youssef, and J. M. Motes, *J. Amer. Chem. Soc.*, **84**, 2466 (1962).

(16) H. E. Zimmerman and D. I. Schuster, *ibid.*, **84**, 4527 (1962), and later papers.

chemistry of a similar compound, 1,3,4,5-tetraphenylbicyclo[3.1.0]hex-3-en-2-one has been studied by Durr.[17] The fact that this compound gives a 91% yield of 2,3,4,6-tetraphenylphenol where phenyl migration has not occurred is again not surprising in terms of the Zimmerman mechanism. Thus the similarity of these photochemical rearrangements also lends support to the structure proposed for IV.

In contrast to the photochemical behavior of the bicyclic ketone IV, the tricyclic ketone I undergoes rearrangement almost exclusively to 2,4,5-triphenylphenol. Masamune and coworkers have proposed and substantiated a mechanism for this photochemical reaction in the case of 1,6-diphenyltricyclo[3.1.0.0^{2,6}]-hexan-3-one.[5d]

Ketone I reacts typically with methylmagnesium iodide to give the corresponding tertiary alcohol (V) whose spectra and analysis agreed with its structure. Compound I also gives derivatives with hydroxylamine, 2,4-dinitrophenyhydrazine, tosylhydrazine, and bromine in carbon tetrachloride, but these products were not fully characterized.



V

We do not intend to explore the chemistry of the title compound further.

Experimental Section

The nmr spectra were run on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Ultraviolet spectra were determined either on a Beckman DK or Cary 14 spectrophotometer with 95% ethanol as the solvent unless otherwise indicated. Infrared spectra were taken as potassium bromide disks on either a Beckman IR-9 or Perkin-Elmer Infracord. Melting points are uncorrected.

(1,2,3-Triphenylcycloprop-2-enyl)acetic Acid (II).—Triphenylcyclopropenyl bromide was prepared by the method of Breslow and Chang[18] and recrystallized from acetonitrile before use.

In a 200-ml, three-necked flask equipped with stirrer, pressure equalizing dropping funnel, and reflux condenser topped with a calcium chloride tube was placed 11 g (0.17 g-atom) of small pieces of zinc which had been sandpapered and then cut and rolled. The system was flamed out and 35 ml of solvent (20 ml of dry benzene and 15 ml of anhydrous diethyl ether) was added. In the dropping funnel was placed 20 ml (30 g, 0.18 mol) of ethyl bromoacetate (Eastman Kodak) in 20 ml of benzene and 10 ml of ether. An iodine crystal was added to the stirred mixture which was heated to reflux. Part of the ethyl bromoacetate solution was added and the reaction mixture turned cloudy after 10 min. Then 5.93 g (0.017 mol) of triphenylcyclopropenyl bromide was added. The remainder of the ethyl bromoacetate solution was added over the course of 30 min. The mixture was allowed to reflux for 3–5 hr. During this time the ether was allowed to evaporate. The homogeneous reaction mixture was poured into water and 6 *N* hydrochloric acid added to dissolve the zinc salts. The reaction mixture was extracted three times with ether; the combined ether layers were washed to neutrality with water, dried over magnesium sulfate, filtered, and removed under reduced pressure to give a reddish oil. This was hydrolyzed directly with 20 g of potassium hydroxide in 250 ml of methanol by refluxing for 100 min. The mixture was poured into water and filtered to collect the fairly insoluble acid salt. The filtrate was extracted two times with ether (discarded), then neutralized with hydrochloric acid and extracted three times with ether which was combined and washed with water, dried over magnesium sulfate, filtered, and removed under reduced pressure. The acid obtained in this manner was combined with the acid obtained by stirring the acid salt overnight with 30 ml of concentrated hydrochloric acid, pouring the mixture into water, extracting with ether, and washing, etc. The crude solid was recrystallized from 50 ml of ethanol to give 3.6 g (59%) of pale yellow crystals, mp 182–184 dec. The yield of acid can be improved slightly by running the reaction under nitrogen. A sample, recrystallized for analysis from ethyl acetate, was colorless and had mp 183° dec.

The infrared spectrum showed a carbonyl band at 1730 and a cyclopropene band at 1835 cm^{-1}. The ultraviolet spectrum had λ_{max} 330 (log ϵ 4.39), 313 (4.47), and a shoulder at 300 mμ (4.34).

Anal. Calcd for $C_{28}H_{18}O_2$: C, 84.63; H, 5.56. Found: C, 84.65; H, 5.55.

1-(1,2,3-Triphenylcycloprop-2-enyl)-3-diazopropan-2-one (III).—Compound II, (1,2,3-triphenylcycloprop-2-enyl)acetic acid, was covered with excess oxalyl chloride and allowed to stand overnight at room temperature. The excess oxalyl chloride was removed under reduced pressure; the resulting solid was dissolved in dry benzene which was then removed under reduced pressure. The acid chloride, dissolved in dry benzene or ether, was added to a stirred solution of a 2-mole excess of diazomethane in ether. The addition (using 1 g of acid chloride in 10 ml of benzene) took about 0.5 hr and the mixture was allowed to stand at room temperature for 2 hr. Removal of the solvent under reduced pressure (do not heat) gave the diazo ketone which was used directly in the synthesis of I. A sample was purified for analysis by recrystallization from carbon tetrachloride. The infrared spectrum showed strong peaks at 2120 (diazo compound), 1820 (cyclopropene), and 1650 cm^{-1} (carbonyl). The ultraviolet spectrum in dioxane had λ_{max} 330 mμ (log ϵ 4.42), 313 (4.50), and 227 (4.59) and a shoulder at 299 mμ (4.41), The nmr spectrum had a 15-proton multiplet centered at 7.5 (phenyl hydrogens), a one-proton singlet at 5.1 (methine hydrogen), and a two-proton singlet at 3.3 ppm (methylene hydrogens).

Anal. Calcd for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 8.00. Found: C, 82.05; H, 5.21; N, 7.91.

1,5,6-Triphenyltricyclo[3.1.0.0^{2,6}]hexan-3-one (I).—A 150-ml, three-necked flask was flamed out and equipped with a reflux condenser, dropping funnel, and nitrogen inlet tube. To the flask was added 30 ml of benzene and 0.9 g of copper powder and the system flushed with nitrogen and brought to reflux. Positive nitrogen pressure was maintained throughout the period of heating. In the dropping funnel was placed 0.992 g of the crude diazo compound III, dissolved in 30 ml of benzene. This was dropped into the refluxing benzene over a period of 10 min and refluxed for 1 hr more. The solution was cooled and filtered free of copper; the benzene was removed under reduced pressure. Chromatography on Fisher alumina (80–200 mesh) gave, in benzene, 0.51 g (57%) with mp 155.5–156° and 0.068 g (7%), with mp 148–156°. A sample prepared for analysis by recrystallization from ethyl acetate had mp 155–157°. The compound rapidly resolidified at its melting point. The infrared spectrum showed a strong carbonyl band at 1750 and a weaker peak at 1710 cm^{-1}. The ultraviolet spectrum (dioxane) showed a shoulder at 243 mμ (log ϵ 4.34). The nmr spectrum had a 15-proton multiplet centered at 7.2 (phenyl hydrogens), a one-proton singlet at 3.2 (bridgehead hydrogen), and a two-proton singlet at 2.6 ppm (methylene hydrogens).

Anal. Calcd for $C_{24}H_{18}O$: C, 89.42; H, 5.63; mol wt, 322. Found: C, 89.24; H, 5.68. mol wt, 318 (thermoelectric osmometer).

Thermal Reaction of 1,5,6-Triphenyltricyclo[3.1.0.0^{2,6}]hexan-3-one (I).—A 40-mg sample of the tricyclic ketone was heated for 1 min under nitrogen in a test tube immersed in an oil bath at 180°. The sample quickly melted and resolidified. The product had mp 227–229. A mixture melting point with an authentic sample of 3,4,5-triphenylphenol[19] which had mp 227–229° was 228–230°. An infrared spectrum was identical with the infrared spectrum of authentic 3,4,5-triphenylphenol.

(17) H. Durr, *Tetrahedron Lett.*, 5829 (1966).

(18) R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, **83**, 2374 (1961).

(19) Prepared by the method of A. Smith [*Chem. Ber.*, **26**, 65 (1893)] as modified by J. B. Garner [*Amer. Chem. J.*, **31**, 143 (1904)]; B. Prager, *et al.*, "Beilsteins Handbuch der Organischer Chemie," Vol. VI, 4th ed, Julius Springer, Berlin, Germany, 1923, p 721; Vol. VIII, p 220.

Rearrangement of I to 4,5,6-Triphenylbicyclo[3.1.0]hex-3-en-2-one (IV).—To 15 ml of purified dioxane and 10 ml of water was added 1.0 g (0.003 mol) of tricyclic ketone I and 1.0 g (0.025 mol) of sodium hydroxide. The resulting mixture was refluxed for 1 hr, then poured into water. The water layer was extracted three times with ether which was washed with water, dried over magnesium sulfate, filtered, and removed under reduced pressure to give an oily solid which was recrystallized from ethanol to give 0.77 g with mp 150–152° and 0.06 g with mp 149–153°. These crops were recombined and recrystallized to give 0.70 g (70%) of colorless, feathery crystals, mp 155–156°. A sample recrystallized for analysis had mp 157–158°. The compound is not stable on silica gel and is sensitive to light.

The compound had a carbonyl band at 1690 cm^{-1} in the infrared and a peak at 1.68 μ in the near infrared. In the ultraviolet it showed λ_{max} 281 mμ (log ϵ 4.14). The nmr spectrum showed a 15-proton multiplet centered at 7.1, a one-proton doublet with some fine structure (J = 1 cps) centered at 5.9 (vinyl proton), a one-proton doublet with some fine structure (J = 4 cps) at 3.1 (cyclopropyl proton), and a one-proton pair of doublets (J = 1 cps, J = 4 cps) at 2.7 ppm (cyclopropyl proton).

Anal. Calcd for $C_{24}H_{18}O$: C, 89.42; H, 5.63; mol wt, 322. Found: C, 89.15; H, 5.68; mol wt, 324 (thermoelectric osmometer).

Photoreaction of IV.—A solution of 0.295 g of IV in 500 ml of 60% dioxane–water in a Pyrex gas bubbler was flushed with nitrogen for 45 min. The system was irradiated in a Srinivasan–Griffin reactor containing 2537-Å lamps for 14 hr. The reaction mixture was reduced in volume to 100 ml by reduced pressure distillation. Water was added and the resulting mixture extracted three times with ether. The ether was extracted with 10% sodium carbonate, acidification of which gave 0.027 g of oil which was not characterized further. The ether was washed with water, dried over magnesium sulfate, filtered, and removed under reduced pressure. Treatment of the resulting oil with ethanol gave 0.027 g (9%) of 3,4,5-triphenylphenol, mp 221–225. Chromatography of the remainder of the material on alumina gave 0.147 g (50%) of crude 2,4,5-triphenylphenol which on recrystallization from petroleum ether (bp 30–60°) gave 0.090 g with mp 97.5–100° and 0.032 g (11%) of 3,4,5-triphenylphenol, mp 195–205°, which on recrystallization from acetonitrile gave 0.011 g, mp 222–224°. The triphenylphenols were characterized by infrared and mixture melting point determinations. Thin layer chromatography revealed that the purified sample of 2,4,5-triphenylphenol contained a trace of 3,4,5-triphenylphenol.

Photoreaction of I.—The photoreaction of 0.290 g of this compound was run the same way as that of compound IV except that it was photolyzed for 22 hr. A slight residue formed (<1%) which was not characterized. A work-up similar to that for the photoreaction of IV gave no acidic fraction. Treatment of the other fraction with ethanol gave 0.143 g (49%) of starting material, mp 155.5–156.5° (identified by mixture melting point and infrared determination). There was left 0.146 g (50%), mp 87–90°, whose infrared spectrum was identical with that of 2,4,5-triphenylphenol. Recrystallization from petroleum ether gave 0.085 g, mp 113–114°. A mixture melting point with authentic 2,4,5-triphenylphenol of mp 114.5–115°[20] was 113.5–115°.

A thin layer chromatogram of the crude reaction product revealed that only starting material and 2,4,5-triphenylphenol were present in large amounts. There were several spots showing traces of other components one of which had the same R_f value as 3,4,5-triphenylphenol. Control reactions, run under the same conditions of temperature, time, concentration, and work-up, revealed that without ultraviolet light neither I nor mixtures of I and 2,4,5-triphenylphenol gave the presumed 3,4,5-triphenylphenol. The other trace spots were present after the photolysis of 2,4,5-triphenylphenol under the same conditions (but not the spot for presumed 3,4,5-triphenylphenol).

Preparation of 2,4,5-Triphenylphenol. 4-Hydroxy-3,4,6-triphenylcyclohex-2-en-1-one.—To a 1-l. round-bottomed, three-necked flask equipped with a mechanical stirrer was added 52 g (0.25 mol) of benzoin, 100 ml of absolute methanol, 100 ml of absolute ethanol, 200 ml of ethylene glycol, and 29 g (0.50 mol) of sodium methoxide. The mixture was stirred until it turned brown. Then 30 g (0.21 mol) of freshly prepared 3-phenyl-3-buten-2-one[21] dissolved in 250 ml of ethanol was added dropwise. As the vinyl compound was added everything dissolved giving a deep reddish purple color. After 14 hr of stirring the reaction mixture was orange and a precipitate had formed. The reaction mixture was poured into a large excess of water and ether and filtered. This gave 50 g (70%) of product, mp 198–201°. A sample recrystallized from ethyl acetate for analysis had mp 212.5–214.5°.

Its infrared spectrum showed a carbonyl band at 1660 cm^{-1}. The ultraviolet spectrum in dioxane had λ_{max} 282 mμ (log ϵ 4.26).

Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.39; H, 5.92.

(2,4,5-Triphenyl)phenyl Acetate.—To 2.4 g (0.007 mol) of 4-hydroxy-3,4,6-triphenylcyclohex-2-en-1-one, mp 206–209°, was added 25 ml of acetic anhydride and 5 drops of concentrated sulfuric acid. The mixture was refluxed for 10 min, then poured into water. The resulting mixture was extracted three times with ether which was washed with water, 10% sodium carbonate, and water and then dried over magnesium sulfate, filtered, and removed under reduced pressure. This gave 2.8 g (109%) of product smelling of acetic acid, mp 153.5–155°. A sample recrystallized for analysis from ethanol had mp 154.5–155.5°. The infrared spectrum showed a carbonyl band at 1750 cm^{-1}. The ultraviolet spectrum had λ_{max} 244 mμ (log ϵ 4.57). The nmr spectrum showed a 17-proton multiplet (phenyl hydrogens) at 7.3 and a three-proton singlet (methyl hydrogens) at 2.1 ppm.

Anal. Calcd for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 85.93; H, 5.70.

2,4,5-Triphenylphenol.—To 1.0 g (0.0028 mol) of acetate was added 50 ml of ethanol and 1.5 g (0.026 mol) of potassium hydroxide. The mixture was boiled for 15 min on the steam bath and allowed to cool slowly to room temperature. The reaction mixture was poured into water, neutralized with hydrochloric acid, extracted three times with ether which was washed with water, dried over magnesium sulfate, filtered, and removed under reduced pressure to give 1.0 g (110%) of product, mp 102–104°. One recrystallization from petroleum ether gave colorless crystals, mp 93–94°.[20] The infrared spectrum showed a peak at 3600 cm^{-1} (hydroxyl). The ultraviolet spectrum showed λ_{max} 308 mμ (log 3.97) and 250 (4.61). The nmr spectrum showed a 17-proton multiplet centered at 7.0 (phenyl hydrogens) and a one-proton singlet at 1.4 ppm (phenolic hydrogen).

Anal. Calcd for $C_{24}H_{18}O$: C, 89.42; H, 5.63. Found: C, 89.23; H, 5.58.

3-Methyl-1,5,6-triphenyltricyclo[3.1.0.0^{2,6}]-3-hexanol (V).—To the Grignard reagent prepared from 1.25 g (0.01 mol) of methyl iodide and 0.25 g (0.01 g-atom) of magnesium in 20 ml of anhydrous ether was added dropwise with stirring 0.300 g (0.00093 mol) of tricyclic ketone I dissolved in 5 ml of benzene. The resulting mixture was stirred 2 min longer and poured into water. The mixture was extracted three times with ether which was washed, dried over magnesium sulfate, filtered, and removed under reduced pressure to give a yellow solid, mp 70–160°. The material was taken up in benzene (some material did not dissolve) and chromatographed on Fisher alumina. Elution with benzene gave 0.234 g of crude solid which on recrystallization from petroleum ether gave 0.075 g (24%) mp 84–90°. The melting point depends on the rate of heating. The infrared spectrum showed a peak in the hydroxyl region.

The nmr spectrum showed a 15-proton multiplet centered at 7.2 (phenyl hydrogens), a one-proton singlet at 2.8 (methine hydrogen), a two-proton singlet at 2.2 (methylene hydrogens), and a three-proton singlet at 1.5 ppm (methyl hydrogens). Apparently, the hydroxyl peak was so broad that it could not be detected.

Anal. Calcd for $C_{25}H_{22}O$: C, 88.72; H, 6.55. Found: C, 88.51; H, 6.68.

Registry No.—I, 1731-34-6; II, 15707-53-6; III, 15707-48-9; IV, 15707-49-0; V, 15746-00-6; 4-hydroxy-3,4,6-triphenylcyclohex-2-en-1-one, 15707-50-3; (2,4,5-triphenyl)phenyl acetate, 15707-51-4; 2,4,5-triphenylphenol, 1731-36-8.

(20) Samples of 2,4,5-triphenylphenol show variable melting points depending on the rate of heating. Rapid heating results in considerably lower melting points. All samples, even those which have been thoroughly dried, show some bubbling on melting. We have not investigated this phenomenon further.

(21) W. Wilson and Z-Y. Kyi, *J. Chem. Soc.*, 1321 (1952).

Acknowledgments.—The author thanks the National Science Foundation and the Institute of Scientific Research, New Mexico Highlands University, for their support in 1963–1964. She wishes to thank Professor Ernest Wenkert for some of the nmr spectra. This research was also partially supported by grants from the Research Corporation, University of Connecticut Research Foundation, and the Petroleum Research Fund. Grateful acknowledgment is made to the donors of these funds.

Strained Organic Molecules. II. Rearrangements of 1-(1,2,3-Triphenylcycloprop-2-enyl)-3-diazopropan-2-one and (1,2,3-Triphenylcycloprop-2-enyl)acetyl Azide[1,2]

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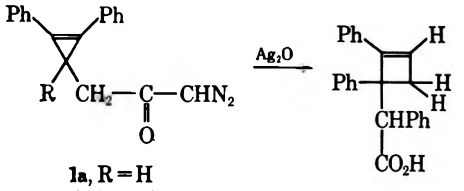
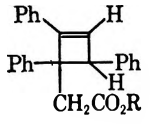
Several reactions are discussed. In the presence of silver benzoate, triethylamine, and ethanol, 1-(1,2,3-triphenylcycloprop-2-enyl)-3-diazopropan-2-one (**1b**) rearranges to two isomers of ethyl (1,2-diphenylcyclobut-2-enyl)phenylacetate (**6a** and **b**). Thermally, (1,2,3-triphenylcycloprop-2-enyl)acetyl azide (**8b**) rearranges to the corresponding isocyanate which was trapped with either dimethylamine or ethanol. With ultraviolet light the azide follows a different pathway.

In the course of our studies on the title rearrangements Masamune and coworkers published several communications[3] on a similar topic. This paper will substantiate and add to the conclusions drawn by his group. The elegant work of Masamune has shown that the product of rearrangement of 1-(1,2,3-triphenylcycloprop-2-enyl)-3-diazopropan-2-one (**1b**) in the presence of silver oxide is to (1,2-diphenylcyclobut-2-enyl)phenylacetic acid (**2**) and not to the tentatively assigned structure, (1,2,4-triphenylcyclobut-2-enyl)acetic acid[1] (**3a**). He also demonstrated that for 1-(2,3-diphenylcycloprop-2-enyl)-3-diazopropan-2-one (**1a**) intermediates in the reaction were 1,2-diphenyltricyclo[2.2.0.0^{2,6}]hexan-3-one (**4a**)[4] and/or phenyl (2-phenylcyclobut-2-enyl)ketene (**5a**).[5]

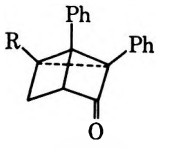


1a, R = H
b, R = Ph

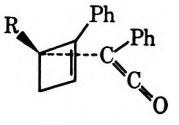
2



3a, R = H
b, R = CH_2CH_3



4a, R = H
b, R = Ph



5a, R = H
b, R = Ph

In addition to the silver oxide conditions for the Wolff rearrangement of **1b**, silver benzoate, triethylamine, and absolute ethanol have also been utilized.[6] Under the latter conditions the rearrangement also takes place and a 48% yield of crude ester **6a** is isolated. The ester was characterized by spectra, which were similar to the corresponding acid, and analysis. In strong base this ester is converted into a new isomeric compound, **6b**. An nmr spectrum of the crude reaction product from the Wolff rearrangement indicates that **6a** and **b** are present in the ratio of roughly 2:1. Under the reaction conditions both **6a** (containing some **6b**) and **6b** remain essentially unchanged so that **6b** must arise from an intermediate and not from **6a**.

The infrared and ultraviolet spectra of **6a** and **b** are very similar. However, the fact that they are different compounds is evidenced in particular by the nmr spectra. First, the chemical-shift values for the various groups are decidedly different for the two compounds. In fact, a weak absorption for the ethyl group in **6b** can be seen clearly in the spectrum of impure **6a**. Moreover, the absorption for the ethyl group in the two compounds is decidedly different. For compound **6a** this absorption is a simple A_2X_3 pattern, whereas for compound **6b** the pattern is that for an ABX_3 system (see Experimental Section). Thus the differing asymmetry of the two molecules affects the nmr pattern for the ethyl group. The conclusion drawn from the spectral and chemical data is that the two compounds must be racemic diastereomers differing in the configuration of the carbon α to the carbonyl group.

The preferential formation of **6a** can be explained by a stereoselective reaction of either 1,2,6-triphenyltricyclo[2.2.0.0^{2,6}]hexan-3-one (**4b**) (postulated in analogy

(1) A preliminary communication of part of this work appeared in A. Small, *J. Amer. Chem. Soc.*, **86**, 2091 (1964).

(2) Abstracted in part from the Master's thesis of S. Tang, University of Connecticut, June 1966.

(3) (a) S. Masamune and N. C. Castellucci, *Proc. Chem. Soc.*, 298 (1964); (b) S. Masamune and K. Fukumoto, *Tetrahedron Lett.*, 4647 (1965); (c) N. C. Castellucci, M. Kato, H. Zenda, and S. Masamune, *Chem. Commun.*, 473 (1967).

(4) A referee has suggested 2,4-diphenyltricyclo[2.2.0.0.^{2,6}]hexan-3-one (i) as an alternative structure to **4a**. With the information available, the authors cannot unequivocably decide between i and **4a**; the nmr data[3b] and

i

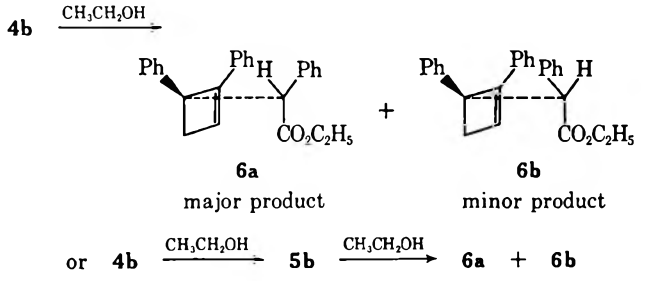
the results of the application of Occam's Razor to the mechanism of formation seem more compatible with **4a**.

(5) For convenience only one member of each *dl* pair is drawn.

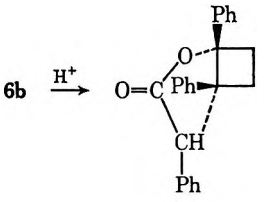
(6) M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.*, **72**, 5163 (1950).

to Masamune's findings[3b]) or the corresponding ketene **5b** with ethanol. These reactions are depicted in Scheme I.[5]

SCHEME I



In addition to the evidence which Masamune has presented for the structure of compound **2** and related compounds[3b] is the rearrangement of **6b** in acid to compound **7** in 91% yield.

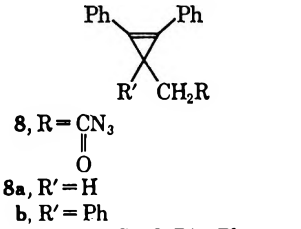


7

Assignment of the structure of **7** rests on its spectra and analysis. The infrared spectrum indicates a γ-lactone (carbonyl band at 1780 cm^{-1}) while the ultraviolet spectrum shows the loss of the phenyl-conjugated double bond (only end absorption). The nmr spectrum substantiates structure **7**. In particular, besides the phenyl absorption, the lowest field absorption was expected to be that for protons on the carbon α to the carbonyl group. This absorption, occurring at 4.4 ppm, is a *one-proton singlet* rather than the complex spectrum expected for the lactone derived from **3b**.

Because of the enlightening chemistry of **1b**, the reactions of (1,2,3-triphenylcycloprop-2-enyl)acetyl azide (**8b**) were studied. During the course of our investigation, Masamune and coworkers reported[3b,c] on the thermal and photoreactions of (2,3-diphenylcycloprop-2-enyl)acetyl azide (**8a**). Our work provides a series of compounds which undergo analogous reactions but unfortunately do not shed any additional light on their mechanisms.

The azide **8b** was prepared from (1,2,3-triphenylcycloprop-2-enyl)acetyl chloride and sodium azide.[7] The azide rearranged thermally in refluxing benzene to the corresponding isocyanate **9**, which could be trapped with dimethylamine to give N,N-dimethyl-N'-(1,2,3-triphenylcycloprop-2-enylcarbinyl)urea (**10**) and with ethanol to give two products, ethyl N-(1,2,3-triphenylcycloprop-2-enylcarbinyl)carbamate (**11**) and 3,4,5-triphenyl-2-pyridone (**12**).[9] The structures of **10** and **11** were straightforwardly assigned on the basis of the



12, R = Ph, R' = H
13, R = H, R' = Ph

typical diphenylcyclopropene chromophore in the ultraviolet spectrum, nmr and infrared spectra, and analysis. The structure of **12** was assigned on the basis of the infrared peaks at 3450 (N—H) and 1630 cm^{-1} (C=O), ultraviolet absorption at λ_{max} 326 mμ (log ϵ 3.92) and 255 (4.33), and analysis. The spectra are qualitatively similar to those reported for 3,4-diphenyl-2-pyridone[3b] and 5,6-diphenyl-2-pyridone[10] and to those for 4,5,6-triphenyl-2-pyridone (see below). The mechanism of pyridone formation in a similar case has been discussed by Masamune.[3c]

Photolysis of **8b** in anhydrous ether gave considerably different results. Besides intractable tars, there was obtained 4,5,6-triphenyl-2-pyridone (**13**). Some **9** was also present (presumably from thermal rearrangement of the azide) which could be trapped with ethanol to give a very low yield of **11**. Irradiation of **9** did not give any **13**. The structure of **13** was indicated by its spectra and analysis (see Experimental Section) and its identity with a sample prepared by a different route.[11] No intermediate was detected in this reaction by removing aliquots and taking nmr and infrared spectra. Masamune[3c] has discussed the mechanism of this reaction with **8a** as starting material.

8, R = CN_2 (=O)
8a, R' = H
b, R' = Ph
9, R = N=C=O; R' = Ph
10, R = NHCN(CH_3)$_2$; R' = Ph
11, R = NHCOCH_2CH_3; R' = Ph

Experimental Section

The nmr spectra were run on a Varian A-60 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. Ultraviolet spectra were determined either on a Beckman DK or Cary 14 spectrophotometer with 95% ethanol as the solvent unless otherwise indicated. Infrared spectra were taken as potassium bromide disks or smears on either a Beckman IR-9 or Perkin-Elmer Infracord. Melting points are uncorrected.

Rearrangement of 1-(1,2,3-Triphenylcyclopropenyl)-3-diazopropan-2-one (1b) to (1,2-Diphenylcyclobut-2-enyl)phenylacetic Acid (2) in Dioxane–Water.—The diazo ketone **1b**, prepared from 1.5 g (0.0046 mol) of (1,2,3-triphenylcycloprop-2-enyl)-acetic acid,[8] was dissolved in 35 ml of purified dioxane and added dropwise with stirring to 0.300 g (0.0013 mole) of silver oxide, 0.510 g (0.0048 mol) of sodium carbonate, and 0.300 g (0.0019 mol) of sodium thiosulfate dissolved in 30 ml of water main-

(7) The chloride was prepared in the usual manner,[8] the azide by the method of W. M. Jones, M. H. Grasley, and W. S. Brey, Jr., *J. Amer. Chem. Soc.*, **85**, 2754 (1963).

(8) See paper I in this series, A. S. Monahan, *J. Org. Chem.*, **33**, 1441 (1968).

(9) A referee has suggested 3,5,6- or 3,4,6-triphenyl-2-pyridone as alternative structures. Although the 3,4,5 arrangement of phenyls is not established by our data, it is the most likely on mechanistic grounds and in view of Masamune's work with **8a**.[3b,d]

(10) A. D. Campbell and K. D. R. Stevens, *J. Chem. Soc.*, 949 (1956).

(11) The synthesis was patterned after the pyridone synthesis of C. Hauser and C. J. Eby, *J. Amer. Chem. Soc.*, **79**, 728 (1957).

tained at 50–60° with an oil bath.[12] The addition took 0.5 hr, and the reaction mixture was heated an additional 0.5 hr. The reacion mixture was filtered and the filtrate extracted three times with ether. The basic filtrate was then acidified with dilute nitric acid and extracted three times with ether. The ether was washed with water, dried over magnesium sulfate, filtered, and removed under reduced pressure to give 0.487 g of oil. Treatment with ethanol gave 0.174 g (11%) of colorless crystals of **2**, mp 175–179, and a second crop of 0.219 g (14%), mp 152–168°.

The ether extracts of the original filtrate were combined, washed with water, dried over sodium sulfate, filtered, and removed under reduced pressure to give 1.09 g of dark oil. This nonacidic material was run through the reaction again using the same quantities of dioxane–water and inorganic reagents and heating at 70–80° for 5.5 hr. Work-up as above gave 0.202 g (13%) of **2**, mp 165–171°.

A sample of **2**, recrystallized for analysis from ethanol, had mp 178.5–180°; ultraviolet, λ_{max} 257 mμ (log ε 4.12); infrared, 1710 cm^{-1} (C=O); nmr, δ 10.1 (s, 1, acid hydrogen), 7.2 (m, 15, phenyl hydrogens), 6.2 (somewhat broad s, 1, vinyl hydrogen), 4.6 (somewhat broad s, 1, tertiary hydrogen), 3.4 (d, 1, J = 14 cps, methylene hydrogen), 2.6 (d, 1, J = 14 cps, methylene hydrogen).

Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.42; H, 5.78.

Rearrangment of 1b to 6a and 6b in Ethanol.—To 1.5 g (0.0043 mol) of **1b** suspended in 60 ml of absolute ethanol was added several drops at a time over a period of 1.5 hr, 0.6 g of silver benzoate dissolved in 6 ml of triethylamine. Most gas evolution ceased after the first 0.5 hr. The reaction mixture was stirred an additional 1.5 hr, poured into water, extracted three times with ether, washed three times with hydrochloric acid, then three times with water, dried over magnesium sulfate, filtered, and removed under reduced pressure to give a red oil. The oil was chromatographed on silica gel to give 0.756 g (48%) of colorless crystalline **6a**, mp 100–106°.

A sample, recrystallized for analysis from ethanol, had mp 98.5–126°; ultraviolet, λ_{max} 256 mμ (log ε 4.13); infrared, 1730 cm^{-1} (C=O); nmr (in addition there were very weak peaks of **6b**), δ 7.3 (m, 16, phenyl hydrogens), 6.5 (t, 1, J = 1 cps, vinyl hydrogen), 4.7 (s, 1, tertiary hydrogen), 3.9 (q, 2, J = 7 cps, methylene of ethyl), 2.7 (q, 1, J = 1 cps, J = 13 cps, ring methylene hydrogen), 0.9 (t, 3, J = 7 cps, methyl hydrogens), 3.5 (d, 0.5, J = 1 cps, upperfield part of quartet due to other ring methylene hydrogen). The lower field portion of the latter absoption is hidden by the quartet at 3.9 ppm.)

Anal. Calcd for $C_{26}H_{24}O_2$: C, 84.75; H, 6.57. Found: C, 84.90; H, 6.50.

To 0.075 g of **6a** was added 25 ml of ethanol containing 6 g of dissolved potassium hydroxide. The mixture was allowed to stand 1 day at room temperature, then poured into water. The water layer was extracted three times with ether which was washed with water, dried over magnesium sulfate, filtered, and removed under reduced pressure. The resulting solid was recrystallized from ethanol to give 0.045 g, mp 130–132°, and a second crop of 0.022 g, mp 95–99°. The first crop, **6b**, recrystallized for analysis from ethanol, had mp 132.5–136°. Admixture with **6a** gave mp 94–124°. The ultraviolet had λ_{max} 259 mμ (log ε 4.18); infrared identical with that of **6a** except that peak at 1200 cm^{-1} was stronger; nmr, δ 7.4 (m, 15, phenyl hydrogens), 6.2 (t, 1, J = 1 cps, vinyl hydrogen), 4.2 (q of d, 2, J = 7 cps, J = 3 cps, methylene of ethyl group), 3.4 (d of d, 1, J = 16 cps, J = 1 cps, ring methylene hydrogen) and 1.1 (t, 3, J = 7 cps, methyl of ethyl group).

Anal. Calcd for $C_{26}H_{24}O_2$: C, 84.75; H, 6.57. Found: C, 84.84, 84.60; H, 6.59, 6.63.

The nmr spectrum of the crude reaction product from another run of the rearrangement of **1b** (acidic material was removed from the ether solution by extraction wih 10% sodium carbonate) was taken. The ratio of the peaks for the methine protons was roughly 2:1 **6a/6b**.

Attempted Equilibration of 6a and 6b under Wolff Rearrangement Conditions.—To a flask was added 0.103 g of **6b**, 0.040 g of silver benzoate, 4 ml of ethanol, and 0.4 ml of triethylamine. Since heat was necessary to keep **6b** in solution, the mixture was refluxed for 0.5 hr and then allowed to stand at room temperature for 2.5 hr during which time a solid precipitated. The reaction mixture was worked up in the same way as the run with compound **1b** except that any acidic material was removed by extraction of the ether solution with two portions of 10% sodium carbonate. The nmr spectrum of the crude product was identical with that of the starting material. No peaks for compound **6a** could be detected.

A 0.102-g sample of **6a**, which by integration of the vinyl and methine hydrogens in the nmr spectrum indicated a ratio of **6a/6b** of 2.2 (±0.2):1, was mixed with 0.040 g of silver benzoate, 4 ml of ethanol, and 0.4 ml of triethylamine. The mixture was warmed to get the solid into solution, then allowed to stand at room temperature for 3.5 hr. After a work-up as for **6b**, the nmr spectrum showed a ratio of **6a/6b** of 2.1 (±0.2):1.

Rearrangement of 6b to Lactone 7.—To 1.011 g (0.00274 mol) of compound **6b**, mp 135–136°, was added 100 ml of acetic acid, 30 drops of water, and 11 drops of sulfuric acid. The mixture was refluxed for 6 hr and poured onto ice. The resulting mixture was extracted three times with ether, which was washed with water, 10% sodium carbonate, and water, dried over magnesium sulfate, filtered, and removed under reduced pressure to give an oily solid. This was recrystallized once from ethanol to give 0.71 g of **7**, mp 129–131°, and 0.126 g, mp 126–131°, or a total of 0.845 g (91%).

A sample, recrystallized for analysis from ethanol, had mp 135–137°; ultraviolet, only end absorption; infrared, 1780 cm^{-1} (C=O); nmr, δ 7.0 (m, 15, phenyl hydrogens), 4.4 (s, 1, tertiary hydrogen), 2.6 (m, 4, methylene hydrogens).

Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92. Found: C, 84.40, 84.49; H, 5.70, 5.86.

(1,2,3-Triphenylcycloprop-2-enyl)acetyl Azide (8b).—The acid chloride[1] from 0.40 g (0.0012 mol) of (1,2,3-triphenylcycloprop-2-enyl)acetic acid, prepared in the usual manner,[8] was dissolved in 8 ml of dry acetone and cooled in an ice bath. To the cold solution was rapidly added 0.080 g (0.0012 mol) of sodium azide dissolved in a minimum amount (about 0.5 ml) of water. The solution was stirred for 1 hr and poured into ice-cold water. The resulting mixture was extracted with ether which was washed once with water, dried over magnesium sulfate at 0°, filtered, and removed under reduced pressure to give **8b**: infrared, 2130 (N=N), 1710 (C=O), and 1800 cm^{-1} (cyclopropene); nmr, δ 7.2 (m, 15, phenyl hydrogens), 3.2 (s, 2, methylene hydrogens). The compound rearranged slowly at room temperature to the corresponding isocyanate **9**.

N,N-Dimethyl-N'-(1,2,3-triphenylcycloprop-2-enylcarbinyl)-urea (10).—An ether solution of **8b** [from 0.3 g of (1,2,3-triphenylcycloprop-2-enyl)acetic acid] was added dropwise to 4 ml of stirred refluxing benzene over the course of 30 min. The solution was refluxed for 20 min more and cooled in an ice bath, and anhydrous dimethylamine passed through for 1 hr. Ether was added to the solution which was washed with water to remove excess dimethylamine, then dried over magnesium sulfate, filtered, and removed under reduced pressure to give 0.294 g of yellow oil. Crystallization from ethyl acetate gave a first crop of 0.044 g of colorless **8b**, mp 118–119°, and a second crop of 0.122 g of yellow crystals, mp 116–120°. The total yield was 0.116 g (49%).

A sample prepared for analysis had mp 120–120.5°; ultraviolet, λ_{max} 330 mμ (log ε 4.32), 315 (4.41), sh 299 (4.34); infrared, 3400 (N–H), 1800 (cyclopropene), 1620 cm^{-1} (C=O); nmr, δ 7.4 (m, 16, phenyl hydrogens and N–H), 4.3 (broad s, 2, methylene hydrogens), 2.6 (s, 6, methyl hydrogens).

Anal. Calcd for $C_{25}H_{24}N_2O$: C, 81.52; H, 6.52; N, 7.60. Found: C, 81.63; H, 6.73; N, 7.85.

Ethyl N-(1,2,3-Triphenylcycloprop-2-enylcarbinyl)carbamate (11) and 3,4,5-Triphenyl-2-pyridone (12).—A dry ether solution of **8b** (from 0.41 g of acid chloride) was added dropwise to 8 ml of refluxing, stirred, dry benzene over the course of 20 min. After the addition was complete, the benzene–ether solution was refluxed for an additional 25 min. The solvent was evaporated and a yellow oil obtained: ultraviolet, λ_{max} 330 mμ (log ε 4.27), 317, 299; infrared, 2275 cm^{-1} (isocyanate). Absolute ethanol (25 ml) was added to the oil and the resulting solution allowed to stand at room temperature for 15 hr. The solvent was removed under reduced pressure to give 0.43 g of brown solid. By fractional crystallization from benzene and ethanol, there was obtained 0.29 g (64%) of **11**, mp 114–116°, and 0.029 g (8%) of **12**, mp 317–320. Another run gave 70% **11**, mp 115–116°, and 6% **12**.

(12) See W. E. Bachmann and W. S. Strove, *Org. Reactions*, **1**, 51 (1942).

A sample of **11**, prepared for analysis by recrystallization from ethanol, had mp 117.5–118°; ultraviolet, λ_{max} 330 mμ (log ε 4.33), 314 (4.43), sh 299 (4.36); infrared, 3300 (N–H), 1800 (cyclopropene), 1690 cm^{-1} (C=O); nmr, δ 7.4 (m, 16, phenyl hydrogens and N–H), 4.3 (d, 2, J = 5 cps, methylene attached to ring), 4.0 (q, 2, J = 7 cps, methylene of ethyl), 1.1 (t, 3, J = 7 cps, methyl of ethyl).

Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.30; H, 6.28; N, 3.79. Found: C, 81.12; H, 6.32; N, 3.75.

A sample of **12** prepared for analysis by recrystallization from acetone had mp 323.5–325°; ultraviolet, λ_{max} 326 mμ (log ε 3.92), 255 (4.33); infrared, 2450 (N–H), 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{17}NO$: C, 85.42; H, 5.30. Found: C, 85.39; H, 5.38.

Photolysis of Azide 8b.—An anhydrous ether solution (200 ml) of **8b** (from 0.35 g of acid chloride) was irradiated in a quartz cell under positive nitrogen pressure. A Srinivasan–Griffin reactor with 2537-Å lamps was used as a light source. The disappearance of the azide bands in the infrared spectrum was complete after 6 hr. After allowing some solvent to evaporate, there was obtained 0.025 g of colorless fluffy crystals, mp 272–275°; a second crop gave 0.013 g, mp 268–271°; a third crop gave 0.008 g, mp 267–271°. The total yield of 4,5,6-triphenyl-2-pyridone (**13**) was 0.046 g (14%). A mixture melting point with **13**, mp 276–277°, prepared by a different route (see below), was 275–276°. The infrared spectra of the two samples were also identical.

A sample prepared for analysis by recrystallization from acetone had mp 276–277°; ultraviolet, λ_{max} 326 mμ (log ε 3.91), 259 (4.25); infrared, 2450 (N–H), 1635 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{17}NO$: C, 85.42; H, 5.30; N, 4.33. Found: C, 85.31; H, 5.30; N, 4.14.

The remainder of the reaction mixture was evaporated to a yellow oil, whose infrared showed a band at 2270 cm^{-1} (isocyanate). Absolute ethanol was added to the oil and after 4 days was removed under reduced pressure. The resulting gum was chromatographed on Fisher adsorption alumina giving 0.005 g (2%) of **11**, mp 115–117°. The rest of the material was an intractable red gum.

Photolysis of 1,2,3-Triphenylcycloprop-3-enylcarbinyl Isocyanate (9).—An anhydrous ether solution of **8b** (from 0.385 g of acid chloride) was added dropwise to 20 ml of refluxing dry benzene over the course of 5 min. It was then refluxed an additional 1 hr. The solvents were evaporated under reduced pressure to give a brown oil whose infrared spectrum showed a band at 2270 cm^{-1}. The oil was dissolved in 200 ml of anhydrous ether and photolyzed for 6 hr. The solvent was evaporated leaving an oil which showed a peak at 2270 cm^{-1} (isocyanate). Absolute ethanol was added to the oil and the solution allowed to stand at room temperature for 4 days. By filtering, 0.032 g (9%) of **12**, mp 315–318°, was obtained. Chromatography of the remaining material on Fisher adsorption alumina gave 5% (0.020 g) of **11**, mp 116–118°. The rest of the material was an intractable red gum.

No pyridone could be obtained before treating the reaction mixture with ethanol.

Preparation of 4,5,6-Triphenyl-2-pyridone (13).[11]—To 75 g of stirred polyphosphoric acid was added 3.6 g (0.025 mol) of 3-phenyl-3-oxopropanenitrile and 5.0 g (0.025 mol) of deoxybenzoin. The mixture was stirred for 5 min and then heated and stirred on a steam bath for 30 min during which time the reaction mixture turned red. Another 5 g of deoxybenzoin was added and the mixture heated at 135–145° in an oil bath for 35 min. The mixture was poured onto 300 g of ice. To this was added 200 ml of ether, and the mixture was stirred for 0.5 hr. The mixture was filtered to give a solid which on recrystallization from acetone gave 0.037 g (0.48%) of **13**, mp 276–277°.

Registry No.—**1b**, 15707-48-9; **2**, 15983-99-0; **6a**, 15983-93-4; **6b**, 15983-94-5; **7**, 15983-95-6; **8b**, 15983-96-7; **10**, 15983-97-8; **11**, 15983-98-9; **12**, 15984-00-6; **13**, 15984-01-7.

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Reactive Intermediates in the Bicyclo[3.1.0]hexyl and Bicyclo[3.1.0]hexylidene Systems. IV.[1] The Free-Radical Chlorination and Chloroformylation of Bicyclo[3.1.0]hexane

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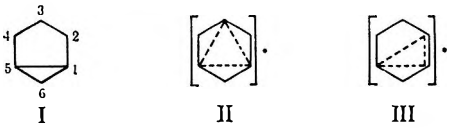
Free-radical chlorination of bicyclo[3.1.0]hexane (I) using *t*-butyl hypochlorite results in substitution at C-2 (78%) and C-3 (22%). Radical chloroformlyation of I using oxalyl chloride generates, after esterification, 2-carbomethoxy- (16%) and 3-carbomethoxybicyclo[3.1.0]hexane (12%) derivatives, as well as rearrangement products methyl Δ^2-cyclopentenylacetate (36%) and 4-carbomethoxycyclohexene (33%).

Our interest in bicyclo[3.1.0]hexyl carbonium ions[1,3] and bicyclo[3.1.0]hexylidene bivalent carbon intermediates[4] led us quite naturally to a consideration of bicyclo[3.1.0]hexyl free-radical intermediates. Hydrogen abstraction from bicyclo[3.1.0]hexane (I) appeared to be a straightforward method of generation of bicyclo[3.1.0]hexyl free radicals. Abstraction of a hydrogen atom from C-3 might produce free radical II,



I II III

analogous to the trishomocyclopropenyl carbonium ion,[5] while abstraction at C-2 might generate radical III, analogous to a bicyclobutonium ion intermediate.[6] We chose to consider free-radical halogenation using

(1) Part III: P. K. Freeman, F. A. Raymond, and M. F. Grostic, *J. Org. Chem.*, **32**, 24 (1967).

(2) Undergraduate research participants, supported by National Science Foundation Grants NSF G-21900 and NSF G-16215.

(3) P. K. Freeman, M. F. Grostic, and F. A. Raymond, *ibid.*, **30**, 771 (1965).

(4) P. K. Freeman and D. G. Kuper, *ibid.*, **30**, 1047 (1965).

(5) (a) S. Winstein, E. C. Friedrich, R. Baker, and Y.-I Lin, *Tetrahedron*, 621 (1966). (b) S. Winstein and J. Sonnenberg, *J. Amer. Chem. Soc.*, **83**, 3235 (1961); **83**, 3244 (1961). S. Winstein, *ibid.*, **81**, 6524 (1959). S. Winstein, J. Sonnenberg, and L. de Vries, *ibid.*, **81**, 6523 (1959).

(6) M. S. Silver, M. C. Caserio, H. E. Rice, and J. D. Roberts, *ibid.*, **83**, 3671 (1961).

t-butyl hypochlorite, which proceeds utilizing the *t*-butoxy radical as the chain carrier,[7] and the lesser known

$$RH + t\text{-}BuO\cdot \longrightarrow R\cdot + t\text{-}BuOH$$
$$R\cdot + t\text{-}BuOCl \longrightarrow RCl + t\text{-}BuO\cdot$$

chloroformylation reaction,[8-12] for which the radical sequence in Scheme I has been proposed.[8]

SCHEME I

I $(COCl)_2 \xrightarrow{h\nu} 2\cdot COCl$

and/or $(COCl)_2 \xrightarrow{h\nu} Cl\cdot + \cdot COCOCl$

II $\cdot COCl \longrightarrow Cl\cdot + CO$

$\cdot COCOCl \longrightarrow Cl\cdot + 2CO$

$RH + Cl\cdot \longrightarrow R\cdot + HCl$

$R\cdot + (COCl)_2 \longrightarrow RCOCl + \cdot COCl$

A different view of the transfer step is favored by Runge[9] and by Treibs and Orttmann (for oxalyl bromide),[11] who support a two-step process, in spite of evidence presented against this alternative.[8] Additional research on this point would appear to be worthwhile.

$$R\cdot + (COX)_2 \longrightarrow RCOCOX + X\cdot$$
$$RCOCOX \longrightarrow RCOX + CO$$

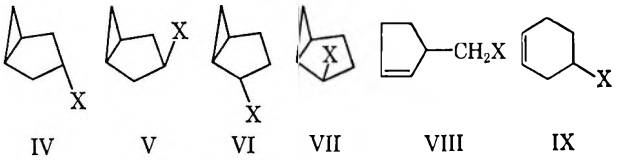
Results

The photochlorination of bicyclo[3.1.0]hexane was accomplished by irradiation of mixtures of bicyclo[3.1.0]hexane (10% mole excess) and *t*-butyl hypochlorite. The yields of monochlorides varied from 24 to 42%. The reaction mixtures were analyzed by vapor phase chromatography, using an 8-ft column of tris(cyanoethoxy)propane, and showed peaks with retention times corresponding to substitution at C-2 and C-3 on the bicyclo[3.1.0]hexane ring skeleton: *trans*-3-chlorobicyclo[3.1.0]hexane (IVa)/*cis*-3-chlorobicyclo[3.1.0]hexane (Va) and/or *trans*-2-chlorobicyclo[3.1.0]hexane (VIa)/*cis*-2-chlorobicyclo[3.1.0]hexane (VIIa) in an average ratio of 7:71:22 (Table I). The *trans*-3 and *cis*-2 chlorides were identified by comparison of their infrared and nmr spectra with those of authentic samples.[1] Comparison of the infrared spectra of the major component (71%) with the spectra of *trans*-2- and *cis*-3-chlorobicyclo[3.1.0]hexane previously recorded[1] demonstrated that the major component was principally the *trans*-2 chloride accompanied by a smaller amount of *cis*-3 chloride in a ratio of 57:14 (base-line calculation using the 747 cm^{-1} *cis*-3 chloride band). Δ^2-Cyclopentenylcarbinyl chloride (VIIIa) and 4-chlorocyclohexene (IXa) have retention times on the tris(cyanoethoxy)propane column corresponding to those for *trans*-3 and *trans*-2 chloride, respectively, but were found not to be present by infrared analyses of the individual component peaks.

TABLE I

PHOTOCHLORINATION OF BICYCLO[3.1.0]HEXANE WITH *t*-BUTYL HYPOCHLORITE

Run	Yield, %	Composition of the monochloride fraction			
		trans-3	*cis*-3	*trans*-2	*cis*-2
1	24	7%	15%	55%	23%
2	35	7	14	57	22
3	40	7	14	57	22
4	34	7	14	56	23
5	30	6	14	57	23
6	35	6	14	57	23
7	42.5	8	13	56	23



IV V VI VII VIII IX

a, X = Cl
b, X = COCl
c, X = CO_2CH_3
d, X = CN

Chloroformylation of bicyclo[3.1.0]hexane was carried out by irradiation of an equimolar solution of oxalyl chloride and bicyclo[3.1.0]hexane. The 15–18% yield of acid chlorides, which was obtained, was converted into a methyl ester fraction by treatment with methanol and pyridine. It was possible to separate two unsaturated components in sufficient purity from the complex mixture of methyl esters by vapor phase chromatography for identification. Infrared and nmr spectral comparison with authentic samples demonstrated that these two components were 4-carbomethoxycyclohexene (IXc) and methyl Δ^2-cyclopentenylacetate (VIIIc). Although the methyl ester fraction resisted all attempts to achieve satisfactory resolution of all components on a variety of vpc columns, adequate resolution of 4-carbomethoxycyclohexene, methyl Δ^2-cyclopentenylacetate, and the remaining carbomethoxybicyclo[3.1.0]hexanes was accomplished by a combination of hydrogenation of the methyl ester fraction over palladium on carbon, a reaction which leaves the bicyclo[3.1.0]hexane skeleton intact, and use of a 25-ft Carbowax 1500 column. Vapor phase chromatographic analysis of this reduced methyl ester fraction and nmr and infrared spectral comparison with standards revealed that the original ester fraction had the composition 36% methyl Δ^2-cyclopentenylacetate (VIIIc), 33% 4-carbomethoxycyclohexene (IXc), and 10% *trans*-3-carbomethoxy-, 2% *cis*-3-carbomethoxy-, 6% *trans*-2-carbomethoxy-, and 10% *cis*-2-carbomethoxybicyclo[3.1.0]hexane (IVc–VIIc).

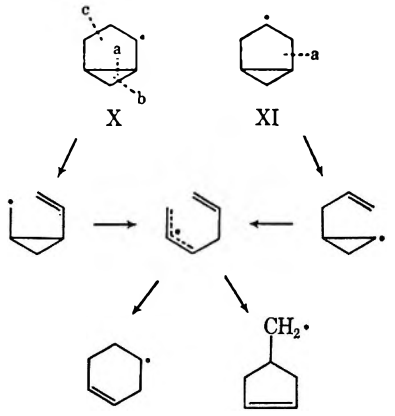
Discussion

In comparing the *t*-butyl hypochlorite chlorination with the chloroformylation, one is first struck with the large degree of rearrangement products (VIIIb, IXb) formed in the latter reaction. The rearrangement pathways leading to these products would appear to be analogous to previously reported examples of β fission

(7) C. Walling and B. B. Jacknow, *J. Amer. Chem. Soc.*, **82**, 6108 (1960).
(8) M. S. Kharasch, S. S. Kane, and H. C. Brown, *ibid.*, **64**, 1621 (1942); **64**, 333 (1942). M. S. Kharasch and H. C. Brown, *ibid.*, **64**, 329 (1942); **62**, 454 (1940).
(9) F. Runge, *Z. Elektrochem.*, **60**, 956 (1956); **56**, 779 (1952).
(10) M. T. Ahmed and A. J. Swallow, *J. Chem. Soc.*, 3918 (1963).
(11) W. Treibs and H. Orttmann, *Naturwissenschaften*, **46**, 85 (1958).
(12) A. I. Gershenovich and A. K. Mikhailova, *Sintez i Svoistva Monomerov, Akad. Nauk SSSR, Inst. Neftekhim. Sinteza, Sb. Rabot 12-oi [Dvenadtsatoi] Konf. po Vysokolomolekul. Soedin.*, 216 (1962); *cf. Chem. Abstr.*, **62**, 6404*d* (1965).

in cyclopropylcarbinyl free-radical systems.[13,14] However, in addition to fission of bonds a and b in cyclopropylcarbinyl radical X, β fission at bond c in X or a in 3-bicyclo[3.1.0]hexyl radical XI might produce cyclopentenylmethyl and 4-cyclohexenyl derivatives (Scheme II). There are, however, no products in either the

SCHEME II



chlorination or chloroformylation reactions, which correspond to the acyclic or monocyclic, cyclopropyl free-radical intermediates of Scheme II. In addition the double bond in the cyclopentenylmethyl radical formed in this manner is in the Δ^3 and not the Δ^2 position. It is possible that a small amount of Δ^3 isomer may have gone undetected in the Δ^2-cyclopentenyl product, however. Walling, Cooley, and coworkers[15] have recently demonstrated the preference of 5-hexenyl and analogous free radicals for cyclization to five-membered ring systems. Although this raises the question as to whether the 4-cyclohexenyl radical might be formed in the above manner, it seems unlikely that the resonance stabilized hexadienyl free radical of Scheme II would undergo ring closure to either of the cyclohexenyl or cyclopentenylmethyl radicals pictured, since the analogous resonance-stabilized intermediate formed by treatment of allyl chloroacetate with tri-*n*-butyltin hydride does not cyclize.[15] Thus the simplest rationalization of product formation in both the chlorination and chloroformylation reactions involves hydrogen abstraction at C-2 and C-3, followed by β fission of the cyclopropane ring, in the case of chloroformylation, as pictured in Scheme III. Slaugh has found that the generation of Δ^2-cyclopentenylmethyl free radical (XIII) by thermal decomposition of *t*-butyl Δ^2-cyclopentenylperacetate in the presence of *p*-cymene or benzotrichloride resulted in a 1,2-vinyl rearrangement producing the 4-cyclohexenyl radical (XV), whereas similar reactions utilizing *t*-butyl 4-cyclohexenylpercarboxylate gave no evidence of rearrangement products.[16] In agreement with the latter finding, Wilt and

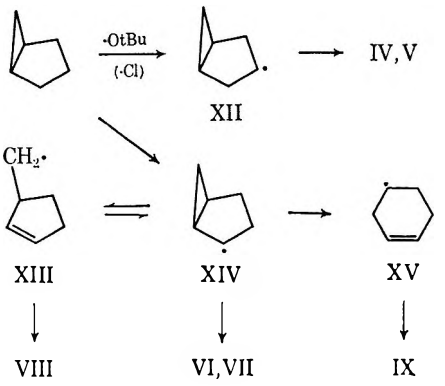
(13) T. A. Halgren, M. E. H. Howden, M. E. Medof, and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 3051 (1967); L. K. Montgomery and J. W. Matt, *ibid.*, **89**, 3050, 934 (1967); L. K. Montgomery, J. W. Matt, and J. R. Webster, *ibid.*, **89**, 923 (1967); D. J. Patel, C. L. Hamilton, and J. D. Roberts, *ibid.*, **87**, 5144 (1965); D. E. Applequist and J. A. Landgrebe, *ibid.*, **86**, 1543 (1964); E. E. Huyser and J. D. Taliaferro, *J. Org. Chem.*, **28**, 3442 (1963); E. Renk, P. D. Shafer, W. H. Graham, R. H. Mazur, and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 1987 (1961).

(14) C. Walling and P. S. Fredricks, *ibid.*, **84**, 3326 (1962); C. Walling and M. F. Mayahi, *ibid.*, **81**, 1458 (1959).

(15) C. Walling, J. H. Cooley, A. A. Ponaras, and E. J. Racah, *ibid.*, **88**, 5361 (1966).

(16) L. H. Slaugh, *ibid.*, **87**, 1522 (1965).

SCHEME III



Levin[17] found no evidence for rearrangement of the 4-cyclohexenyl free radical produced by decarbonylation of 4-cyclohexenylcarboxaldehyde. It appears, then, that some equilibration of Δ^2-cyclopentenylmethyl and 2-bicyclo[3.1.0]hexyl free radicals may be established during the chloroformylation reaction, but equilibration of the 4-cyclohexenyl and 2-bicyclo[3.1.0]hexyl radical intermediates seems unlikely. Furthermore, our results lend support to the mechanistic alternative suggested by Slaugh for rearrangement of the cyclopentenyl radical XIII to cyclohexenyl radical XV *via* bicyclohexyl intermediate XIV.

Since the chlorination and chloroformylation reactions have been carried out at reaction temperature ranges which were not too divergent (*ca.* 70–85° and 70–100°, respectively), the greater degree of rearrangement in the case of chloroformylation appears to be most simply explained on the basis of a smaller transfer constant relative to that for the reaction of radical XIV with *t*-butyl hypochlorite. This necessarily leads to the presentation of the fate of the radical intermediate formed by hydrogen abstraction at C-2 in terms of classical radicals XIII, XIV, and XV (Scheme III), rather than in terms of a single nonclassical radical such as XVI.[18]

XVI

Basing our analysis of product formation on Scheme III, we find no evidence for C-1 or C-6 abstraction. This is not surprising in view of the relative reactivities of cyclopentane and cyclopropane to hydrogen abstraction by ·OtBu and ·Cl as reported by Walling.[14] The total lack of free-radical bridgehead substitution in these reactions of bicyclo[3.1.0]hexane provides a substitution pattern similar to that found for norbornane[19] and bicyclo[2.1.1]hexane,[20] rather than bicyclo[2.2.0]hexane[21] and bicyclo[1.1.1]pentane[22] (Table II). An interesting facet of the chlorination and chloroformylation of bicyclo[3.1.0]hexane is the preference

(17) J. W. Wilt and A. A. Levin, *J. Org. Chem.*, **27**, 2319 (1962).

(18) This picture is consistent with the results of a study of radical intermediates generated by free-radical addition of methyl mercaptan to bicyclo[3.1.0]hexene-2: P. K. Freeman, M. F. Grostic, and F. A. Raymond, unpublished results, University of Idaho.

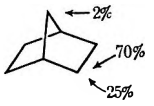
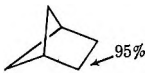
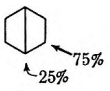
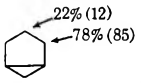
(19) E. C. Kooyman and G. C. Vegter, *Tetrahedron*, **4**, 382 (1958).

(20) R. Srinivasan and F. I. Sonntag, *J. Amer. Chem. Soc.*, **89**, 407 (1967).

(21) R. Srinivasan and F. I. Sonntag, *Tetrahedron Lett.*, 603 (1967).

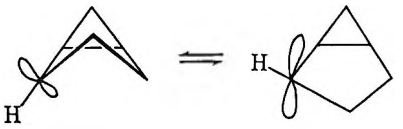
(22) K. B. Wiberg and D. S. Connor, *J. Amer. Chem. Soc.*, **88**, 4437 (1966).

TABLE II
FREE-RADICAL SUBSTITUTION PATTERNS IN SOME BICYCLOALKANES

Substrate	Reacn conditions	Ref
	Cl_2, $h\nu$, CH_2Cl_2, 42°	*a*
	Cl_2, $h\nu$, CCl_4, 77°	*b*
	Cl_2, $h\nu$	*c*
	*t*-BuOCl, $h\nu$, 0°	*d*
	*t*-BuOCl, $h\nu$, 70–85° (ClOCCOCl, $h\nu$, 70–100°)	This work

[a] See ref 19. [b] See ref 20. [c] See ref 21. [d] See ref 22.

for C-2 over C-3 hydrogen abstraction. Correcting for the fact that substitution at C-2 is favored statistically over C-3, the ratio of C-2/C-3 hydrogen abstraction (per hydrogen) for ·OtBu is 1.8:1, while chloroformylation gives a C-2/C-3 abstraction ratio (per hydrogen) of 3.6:1. The preference for C-2 over C-3 abstraction occurs in spite of the electron-withdrawing polar effect of cyclopropane,[23] which should promote C-3, rather than C-2 abstraction[24] for electrophilic radicals such as ·OtBu[25] and ·Cl.[24,26] The resonance effect of the cyclopropane ring must, therefore, be responsible for the preference for hydrogen abstraction at C-2. Since electrophilic radicals are involved in both reactions, the transition state for abstraction would be expected to be polarized conferring some carbonium ion character upon the developing hydrocarbon fragment, which should contribute to a preference for C-2 abstraction.[1,3] In this regard, it is interesting that inspection of a Dreiding model reveals that the 2-bicyclohexyl free radical can achieve the bisected conformation (XVII) preferred for cyclopropylcarbinyl free radicals with excess charge $q_i \geq 0$[27] by puckering C-3 toward the cyclopropane ring to form a boat-shaped conformation. In fact, little conformational adjustment would be required for production of XVII, since the most stable conformation for the starting hydrocarbon, bicyclo[3.1.0]hexane, appears to be a boat-shaped structure.[28] On balance, a boat conformation for free radical XVII also appears to relieve nonbonded interactions more effectively, relative to a planar cyclopentane configuration, than the conformation obtained by puckering C-3 in the opposite direction (XVIII).[29]



XVII XVIII

In addition to a consideration of the preference for C-2 over C-3 hydrogen abstraction in both chlorination and chloroformylation, a comparison of the difference in the apparent selectivities for C-2/C-3 hydrogen abstraction for ·OtBu (1.8:1.0) and ·Cl (3.6:1.0) is of interest. Since the reaction temperature ranges for chlorination and chloroformylation are not too widely different, and since the selectivity of the *t*-butoxy radical appears to be insensitive to temperature changes between 40 and 135°,[30] the differences in selectivity for the abstracting radicals are due to their inherent characteristics. The fact that ·OtBu appears to be less selective than Cl·, in contrast to the usual order observed,[31,32] suggests that Cl· may not be the only H-transfer agent involved in chloroformylation or that ·Cl may be complexed with oxalyl chloride.[32]

One final feature of Table I is particularly intriguing. The 2:1 ratio of *cis*-3/*trans*-3 substitution found, in spite of the steric blocking of *cis* approach by the cyclopropane methylene, provides a hint that anchimeric assistance to *cis*-C-3 hydrogen abstraction, analogous to that observed in the solvolysis of the *cis*-3-tosylate,[5] may play a role. Further experimentation along this line is in progress.

Experimental Section[33]

Preparation of Bicyclo[3.1.0]hexane.—Bicyclo[3.1.0]hexane was prepared by the method of Simmons and Smith.[34] The infrared spectra exhibit the typical bicyclo[3.1.0]hexyl high energy C–H stretching frequencies at 3055, 3025, and 2995 cm^{-1} and a cyclopropyl absorption band at 1022 cm^{-1}. The nmr spectrum shows high field cyclopropyl methylene protons in the region τ 9.60–10.00 and a complex absorption for the other eight protons in the region τ 8.00–9.23.

Chlorination of Bicyclo[3.1.0]hexane with *t*-Butyl Hypochlorite.—A mixture of bicyclo[3.1.0]hexane (2.50 g, 30.5 mmol) and *t*-butyl hypochlorite[35] (3.00 g, 27.6 mmol) was irradiated with a General Electric sun lamp until a gentle reflux was obtained. Upon completion of the spontaneous reaction the mixture was irradiated for an additional period of 2–3 min to ensure completion of the reaction (reaction temperature *ca.* 70–85°). The reaction mixture (5.31 g) was analyzed by vpc using a 30-ft copper column of 30% Carbowax 1500 on Chromosorb P at 135°. The over-all yield of monochlorides was calculated to be 34% on the basis of vpc data. The area of the chromatogram representing the monochlorides in a known amount of reaction mixture was

(23) T. L. Brown, *J. Amer. Chem. Soc.*, **80**, 6489 (1958).

(24) G. A. Russell and A. Ito, *ibid.*, **85**, 2983 (1963); G. A. Russell, A. Ito, and R. Konaka, *ibid.*, **85**, 2988 (1963).

(25) H. Sakurai and A. Hosomi, *ibid.*, **89**, 458 (1967).

(26) G. A. Russell and R. C. Williamson, Jr., *ibid.*, **86**, 2357 (1964).

(27) G. A. Russell and H. Malkus, *ibid.*, **89**, 160 (1967); N. L. Bauld, R. Gordon, and J. Zoeller, Jr., *ibid.*, **89**, 3948 (1967).

(28) Winstein and coworkers[5a] have presented nmr spectral evidence for a preferred boat conformation for both *cis*- and *trans*-3-bicyclo[3.1.0]hexyl derivatives. We have come to a similar conclusion as a result of consideration of nmr data of *trans*-2-bicyclo[3.1.0]hexyl substrates.[1,3] It thus seems entirely likely that the most stable conformation for the parent hydrocarbon, bicyclo[3.1.0]hexane, is also the boat form.

(29) Conformation XVII relieves the nonbonded interactions between the hydrogens at *cis*-C-4 and *syn*-C-6 and *trans*-C-4 and C-5, and increases interaction between hydrogens at C-1 and C-2, while conformation XVIII achieves the converse.

(30) W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., New York, N. Y., 1966, p 167.

(31) C. Walling and W. Thaler, *J. Amer. Chem. Soc.*, **83**, 3877 (1961); G. A. Russell, *ibid.*, **80**, 4997 (1958).

(32) G. A. Russell, *ibid.*, **80**, 4987 (1958).

(33) Infrared spectra were determined as pure liquids using Perkin-Elmer Models 137 and 237 spectrophotometers. Nmr spectra were run in carbon tetrachloride with tetramethylsilane as the internal reference using a Varian Associates A-60 nmr spectrometer. Gas chromatographic analyses were performed using either an Aerograph Model A-700 or Model A-90-P chromatograph, and helium was used as the carrier gas. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn., and by Max Bernhardt, Mikroanalytisches Laboratorium, Max-Planck Institute, Mülheim, Germany.

(34) H. E. Simmons and R. D. Smith, *ibid.*, **81**, 4256 (1959).

(35) H. M. Teeter and E. W. Bell, *Org. Syn.*, **32**, 20 (1952).

compared with the peak areas of known amounts of 4-chlorocyclohexene. Numerous vpc columns were tested and the one which was found to be most satisifactory for analysis of this mixture of chlorides was an 8-ft aluminum column of 13% tris(cyanoethoxy)-propane (TCEP) on HMDS-treated Chromosorb W. Vpc analysis using this column, coupled with spectral comparison with authentic samples,[1] gave the following reaction composition in one typical run (see Table I): 7% *trans*-3-chlorobicyclo[3.1.0]hexane, 14% *cis*-3-chlorobicyclo[3.1.0]hexane, 57% *trans*-2-chlorobicyclo[3.1.0]hexane, and 22% *cis*-2-chlorobicyclo[3.1.0]-hexane. The compounds had the following retention times on the TCEP column at a column temperature of 70° and a flow rate of *ca.* 60 ml/min: *trans*-3-chlorobicyclo[3.1.0]hexane, 10.0 min; *cis*-3- and *trans*-2-chlorobicyclo[3.1.0]hexane, 12.1 min; *cis*-2-chlorobicyclo[3.1.0]hexane, 16.0 min. Δ^2-Cyclopentenylcarbinyl chloride and 4-chlorocyclohexene had retention times corresponding to those for *trans*-3 and *trans*-2 chloride, respectively, but were found not to be present by infrared analysis of the individual peaks. The percentage of *cis*-3-chlorobicyclo-[3.1.0]hexane in *trans*-2-chlorobicyclo[3.1.0]hexane was determined by infrared analysis (base-line calculation at 747 cm^{-1}).

Chloroformylation of Bicyclo[3.1.0]hexane.—A mixture of 19.2 g (0.151 mol) of oxalyl chloride and 12.4 g (0.151 mol) of bicyclo-[3.1.0]hexane was irradiated, under nitrogen, with a General Electric sun lamp, held approximately 1 in. from the reaction flask, for 46 hr. The reaction mixture was stirred during this period with a magnetic stirring bar; the heat from the sun lamp caused the reaction mixture to reflux gently (reaction temperature was *ca.* 70–100°). After the irradiation period was complete, the reaction mixture was distilled and 3.40 g (15.6% yield), bp 75–120° (30 mm), of acid chlorides was obtained. The acid chlorides were converted into methyl esters by treatment with methanol and pyridine.

The use of a 25-ft Carbowax 1500 vapor phase chromatographic column allowed the partial resolution of two of the seven components ultimately determined to be present. Infrared comparison with authentic samples demonstrated that these two components, the two most abundant products, were methyl Δ^2-cyclopentenylacetate and 4-carbomethoxycyclohexene. It was discovered that hydrogenation of the methyl ester product fraction over palladium-on-carbon catalyst reduced the cyclopentene and cyclohexene esters and that the corresponding saturated products had somewhat shorter retention times on a 25-ft Carbowax 1500 column. The combination of reduction and use of the Carbowax column allowed a separation of the cyclopentane and cyclohexane esters from the bicyclo[3.1.0]hexane esters and determination of product composition: 36% methyl Δ^2-cyclopentylacetate, 33% 4-carbomethoxycyclohexane, 10% *cis*-2-carbomethoxybicyclo[3.1.0]hexane, 6% *trans*-2-carbomethoxybicyclo[3.1.0]hexane, 2% *cis*-3-carbomethoxybicyclo[3.1.0]-hexane, 10% *trans*-3-carbomethoxybicyclo[3.1.0]hexane, and 3% unidentified component. In two additional experiments, subjection of bicyclo[3.1.0]hexane and a mixture of methyl Δ^2-cyclopentenylacetate and 4-carbomethoxycyclohexene to the reduction conditions demonstrated that conditions sufficient for complete reduction of the unsaturated esters left the bicyclo-[3.1.0]hexane skeleton intact.

***cis*- and *trans*-2-Cyanobicyclo[3.1.0]hexane.**—To a stirred mixture of potassium cyanide (1.6 g, 25 mmol) in 2.6 ml of aqueous acetone (54% water by volume) was added 1.0 g of *cis* and *trans*-2-chlorobicyclo[3.1.0]hexane (60:40). After 30 hr of stirring, the reaction mixture was diluted with about 10 ml of water and the nitriles were extracted with several 15-ml portions of ether. After drying over anhydrous magnesium sulfate, the ether was removed at reduced pressure, using a rotary evaporator, to yield 1.03 g of crude product. Vpc analysis using a 10-ft aluminum column of 25% Carbowax 1500 on Chromosorb P (flow rate *ca.* 60 ml/min. and a column temperture of 150°) showed the crude product to be 52% nitriles, 27% alcohols, and 21% residual chlorides. The nitriles were shown to be *trans*-2-cyanobicyclo[3.1.0]hexane, 4-cyanocyclohexene and *cis*-2-cyanbicyclo[3.1.0]hexane in the ratio of 48:7:45. The retention times were 16.3, 18.7, and 20.9 min, respectively, on the 10-ft Carbowax 1500 column, using the flow and temperature listed above.

Anal. Calcd for C_7H_9N: C, 78.48; H, 8.46. Found for *cis*-2 nitrile: C, 78.35; H, 8.49. Found for *trans*-2 nitrile: C, 78.43; H, 8.60.

The nmr spectrum of the *trans*-2-cyanobicyclo[3.1.0]hexane shows typical high field absorption for cyclopropane methylene (τ 9.30–10.00) for *trans* isomers, a complex splitting pattern for six protons in the region τ 7.60–8.90 and a doublet centered at 7.13 (J = 7.1 cps). The infrared spectra show typical bicyclo-[3.1.0]hexane[1,3] C–H stretching frequencies at 3070, 3030, and 3000, a cyclopropyl absorption band at 1025, and a nitrile absorption band at 2250 cm^{-1}.

The nmr spectrum of *cis*-2-cyanobicyclo[3.1.0]hexane shows typical high field absorption for cyclopropane methylene (τ 9.23–9.63) for *cis* isomers, a complex splitting pattern for six protons in the region 7.69–8.82 and a sextet for the proton α to the cyano group in the region 6.78–7.30. The infrared spectra show typical bicyclo[3.1.0]hexane C–H stretching frequencies at 3000, 3030, and 3070, a cyclopropyl absorption band at 1025, and a nitrile band at 2250 cm^{-1}. The 3030-cm^{-1} band is enhanced in the *cis* isomer relative to that for the *trans* isomer. The infrared spectra of 4-cyanocyclohexene show high energy C—H stretching frequency at 3030, a C=C band at 1650, and a nitrile band at 2250 cm^{-1}.

The alcohols were identified as *trans*-2-bicyclo[3.1.0]hexanol, *cis*-2-bicyclo[3.1.0]hexanol, and 4-hydroxycyclohexene in the ratio of 55:9:36. The alcohol fraction exhibited two peaks on a 10-ft Carbowax 1500 column (flow rate *ca.* 60 ml/min, column temperature 150°). The retention times for the two peaks were 10.6 and 11.4 min corresponding to those for *trans*- and *cis*-2 alcohols in a ratio of 55:45. The infrared spectrum of the 55% peak showed it to be *trans*-2-bicyclo[3.1.0]hexanol when compared with the spectrum of an authentic sample. The infrared spectrum of the 45% peak showed it to be predominantly 4-cyclohexenol. Since the 45% peak could not be collected pure, the amount of 4-cyclohexenol was determined from the mixture of all three alcohols collected from an XF-1150 column as one peak. Using the C=C band at 1650 cm^{-1} and the 735-cm^{-1} bands, the amount of 4-cyclohexenol in the mixture was determined to be 36%.

Preparation of *cis*-3-Cyanobicyclo[3.1.0]hexane. A. In Acetone.—To a stirred mixture of 2.3 g (35 mmol) of potassium cyanide in 35 ml of acetone was added 3.5 g (30 mmol) of *cis*- and *trans*-3-chlorobicyclo[3.1.0]hexane (76:24). The reaction was stirred at room temperature for 8 hr and vpc analysis on a 10-ft copper column of 25% nitrile silicone fluid XF-1150 on Chromosorb P (flow rate *ca.* 50 ml/min, column temperature 150°) showed no sign of reaction. The reaction was refluxed for 8 hr, after which the salts were filtered off and the acetone was removed by evaporation at reduced pressure to yield 4.45 g of crude material containing some acetone. Vpc analysis of the recovered material on the 10-ft XF-1150 column showed it to be *cis*- and *trans*-3-chlorobicyclo[3.1.0]hexane having the same ratio (76:24) as in the starting material.

The recovered material was added to 45 ml of aqueous acetone (80% water by volume) containing 3.0 g (46 mmol) of potassium cyanide. After 35 hr of heating at reflux, the reaction mixture was extracted with ether and the ether layer was dried over anhydrous magnesium sulfate. Evaporation of the solvents at reduced pressure yielded 1.65 g of crude product. This product showed residual chloride (33%) (in the ratio of 41:39 for *cis*,*trans*), *cis*-3-bicyclo[3.1.0]hexanol (27%), and *cis*-3-cyanobicyclo[3.1.0]hexane (40%). The *cis*-3-bicyclo[3.1.0]hexanol was identified by retention time on an XF-1150 column and the identification of the *cis*-3-cyanobicyclo[3.1.0]hexane is described below.

B. In Aqueous Acetone.—To a stirred mixture of 9.00 g (0.14 mol) of potassium cyanide in 13.5 ml of 60% aqueous acetone was added 6.00 g of *cis*- and *trans*-3-chlorobicyclo[3.1.0]-hexane (74:26). After heating at reflux for 3 days, the reaction mixture was diluted with 25 ml of water and extracted several times with 20–30-ml portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and the ether was removed under reduced pressure yielding 4.80 g of crude material. Vpc analysis of the crude material on the 10-ft XF-1150 column (flow rate *ca.* 60 ml/min, column temperature 150°) showed it to be 21% unreacted 3 chlorides (97:3 for *trans*,*cis*), 7% *cis*-3-bicyclo[3.1.0]hexanol, and 72% *cis*-3-cyanobicyclo-[3.1.0]hexane. The crude material was distilled on an 18-in. semimicro spinning-band distillation column to yield 2.52 g of a mixture containing *cis*- and *trans*-3 chlorides, *cis*-3 alcohol, and *cis*-3 nitrile, bp 80–105° (50 mm), and 1.05 g of *cis*-3 nitrile forced over by reducing the pressure. The *cis*-3-cyanobicyclo-[3.1.0]hexane was further purified by collecting it from a 10-ft XF-1150 column, for infrared, nmr, and carbon–hydrogen analysis.

Anal. Calcd for C_7H_9N: C, 78.48; H, 8.46. Found: C, 78.36; H, 8.42.

The structure of the one 3-cyanobicyclo[3.1.0]hexane isomer obtained was determined by nmr and infrared analyses. The nmr spectrum exhibits typical high field absorption (τ 9.20–9.60) for a bicyclo[3.1.0]hexane derivative substituted with an electronegative *cis*-3 substituent, a complex band for two tertiary protons on a cyclopropane ring in the region τ 8.38–8.75, a complex splitting pattern for four methylene protons in the region 7.50–8.05, and a complex splitting pattern for the proton α to the nitrile group in the region 6.86–7.30. The splitting pattern for the two methylene protons (τ 9.20–9.60) of the cyclopropane ring, as well as being shifted downfield relative to the parent hydrocarbon, falls into the same splitting pattern as those for the analogous protons of the *cis*-3 alcohol, *cis*-3 methyl ether, and the *cis*-3 thioether. The splitting pattern for the four methylene protons (τ 7.50–8.05) is similar to the pattern found for the same protons in the *cis*-3 alcohol and *cis*-3 methyl ether. These splitting patterns mentioned for the *cis*-3 isomers are quite different from those found in the corresponding *trans* isomers.

The infrared spectra show typical bicyclo[3.1.0]hexyl C–H stretching frequencies at 3005, 3040, and 3070, a cyclopropyl absorption band at 1030, and a nitrile band at 2230 cm^{-1}. The 3040-cm^{-1} band is the strongest band of the three C–H stretching frequencies and this reinforces the *cis*-3 assignment based on nmr spectral analysis.[1,3]

Preparation of *cis*- and *trans*-2-Carbomethoxybicyclo[3.1.0]-hexane.—To 771 mg (7.2 mmol) of nitriles (*cis*- and *trans*-2 nitrile and 4-cyanocyclohexene, 27:63:10) and 230 mg of methyl alcohol was added 260 mg of dry hydrogen chloride without cooling. Upon placing in an ice bath, the reaction mixture solidified. After several hours the imino ether hyrochlorides were hydrolyzed to the methyl esters by adding an excess of water and stirring for several hours. The esters were extracted with ether and the ether extracts were washed with 0.1 *N* NaOH to extract any acid formed during isolation of the products. After washing with distilled water, the ether extracts were dried over magnesium sulfate. Removal of the ether yielded 0.63 g of methyl esters. Analysis of the esters using a 30-ft aluminum column of 25% Carbowax 1500 (flow rate *ca.* 60 ml/min, column temperature 130°) showed three peaks in the ratio of 73:20:7 with retention times of 34.4, 36.8, and 38.7 min. The peaks were identified as *trans*-2-carbomethoxybicyclo[3.1.0]hexane, *cis*-2-carbomethoxybicyclo[3.1.0]hexane, and 4-carbomethoxycyclohexene, respectively.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.56; H, 8.63. Found for *cis*-2 ester: C, 68.44; H, 8.62. Found for *trans*-2 ester: C, 68.45; H, 8.61.

The nmr spectrum of *cis*-2-carbomethoxybicyclo[3.1.0]hexane shows high field absorption (τ 9.40–9.90) for cyclopropane methylene, a complex splitting pattern for six protons in the region 7.80–9.00, a complex splitting pattern for the *trans*-2 proton (α to the carbomethoxy group) in the region 6.92–7.35, and a O-methyl singlet at 6.37. The infrared spectra show typical bicyclo[3.1.0]hexyl C—H at 3070, 3035, and 3005, a cyclopropyl band at 1020, an ester C=O band at 1730, and a C—O band in the region 1140–1200 cm^{-1}. The 3035-cm^{-1} band is enhanced relative to the analogous band in the *trans* epimer.

The nmr spectrum of *trans*-2-carbomethoxybicyclo[3.1.0]-hexane shows typical high field absorption (τ 9.37–10.00) for cyclopropane methylene of *trans*-2-bicyclo[3.1.0]hexyl derivatives, a complex splitting pattern for six protons in the region 7.74–8.92, a doublet centered at 7.23 (J = 7.8 cps), and a O-methyl singlet at 6.37. The doublet at τ 7.23 is characteristic of *trans*-2-bicyclo[3.1.0]hexyl derivatives. The infrared spectra show typical bicyclohexyl C—H stretching frequencies at 3000, 3030, and 3070, a cyclopropyl band at 1020, an ester C=O band at 1730, and the C—O band in the region 1140–1200 cm^{-1}.

Preparation of *cis*- and *trans*-3-Carbomethoxybicyclo[3.1.0]-hexane.—The imino ether hydrochloride was prepared by adding 160 mg of dry hydrogen chloride to a mixture of 494 mg of *cis*-3-cyanobicyclo[3.1.0]hexane and 150 mg of methanol in an ice bath. After the imino ether hydrochloride had solidified, about 6 hr, it was hydrolyzed to the methyl esters by adding an excess of water. The esters were extracted with ether and the ether layer was washed with several milliliters of 0.1 *N* NaOH and a few milliliters of distilled water and then dried over anhydrous magnesium sulfate. Evaporation of the ether yielded 400 mg of the bicyclic esters. Analysis using a 30-ft aluminum column of 25% Carbowax 1500 on Chromosorb P (flow rate *ca.* 60 ml/min, column temperature 155°) showed two peaks at 25.0 and 28.0 min in the ratio of 73:27 for *cis*- and *trans*-3-carbomethoxybicyclo-[3.1.0]hexane.

The nmr spectrum of the *trans*-3-carbomethoxybicyclo[3.1.0]-hexane shows high field absorption (τ 9.48–10.08) for cyclopropane methylene, a complex splitting pattern for two tertiary protons on a cyclopropane ring in the region 8.50–8.87, a complex splitting pattern for five protons in the region 7.35–8.40, and an O-methyl singlet at 6.42. The *cis*-3 proton undoubtedly contributes to the lower part of the τ 7.35–8.40 region. The infrared spectra show typical bicyclo[3.1.0]hexyl C—H stretching frequences (for *trans* isomers) at 3000, 3030, and 3070, an ester C=O at 1740, C—O band at 1100–1210, and a cyclopropyl absorption band at 1020 cm^{-1}.

The nmr spectrum of the *cis*-3-carbomethoxybicyclo[3.1.0]-hexane shows a high field absorption (τ 9.40–10.15) for cyclopropane methylene, a complex splitting pattern for the two tertiary protons on a cyclopropane ring in the region 8.57–8.95, an absorption band for the four C-2 and C-4 protons at 7.6–8.3, a complex splitting pattern for the *trans*-3 proton α to the carbomethoxy group in the region 6.88–7.40, and an O-methyl singlet at 6.41. The infrared spectral show typical bicyclo[3.1.0]hexyl C—H stretching frequencies (for *cis* isomers) at 3000, 3035, and 3070, an ester C=O band at 1745, a C—O band at 1160–1220, and a cyclopropyl band at 1030 cm^{-1}.

It is surprising that the methylene protons on the cyclopropyl ring have such unusually high absorption in the case of the *cis* isomer. The structural assignment was based on the enhancement of the 3030-cm^{-1} band in the infrared spectra for the *cis* isomer and the fact that the absorption for the C-3 proton (α to carbomethoxy) occurs at higher field in the *trans*-3 epimer. This is ascribed to the anisotropic shielding effect of the cyclopropane ring[36] which would be expected to shield the *cis*-C-3 proton. Shielding of the *cis*-C-3 proton has been noted for all 3-bicyclo[3.1.0]hexyl epimeric pairs studied so far.[37] Finally the nmr spectrum of the isomer assigned as *cis* is identical with the nmr spectrum published by Gassman and Zalar for *cis*-3 methyl ester, and, in addition, the infrared spectra of *cis*-3 and *trans*-3 methyl esters prepared by this procedure match those obtained in Professor Gassman's laboratory.[38]

Registry No.—I, 285-58-5; IVc, 5861-26-7; Vc, 1777-47-5; Vd, 15733-78-5; VIc, 15733-77-4; VId, 15733-75-2; VIIc, 15733-76-3; VIId, 15815-98-2.

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(36) K. Tori and K. Kitahonoki, *J. Amer. Chem. Soc.*, **87**, 386 (1965).
(37) F. A. Raymond, Ph.D. Thesis, University of Idaho, 1965.
(38) P. G. Gassman and F. V. Zalar, *Tetrahedron Lett.*, **44**, 3251 (1964). We thank Professor Gassman for providing us with infrared spectra of *cis*- and *trans*-3-carbomethoxybicyclo[3.1.0]hexane.

Synthesis of Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (Homocubane) and Some of Its Derivatives[1]

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Homocubane-4-carboxylic acid (6) has been prepared by two routes both of which utilize a Favorskii-type ring contraction of an α-halo ketone to generate the homocubane skeleton. In the preferred route, ketone **5**, formed by photochemical ring closure of the Diels–Alder adduct, **4**, of cyclopentadiene and α-bromocyclopentadienone, gave acid **6** (in nearly quantitative yield) when heated with aqueous alkali. In the alternate route, ketone **7**, when heated with solid sodium hydroxide in benzene, gave a mixture of ring cleaved acid **8a** and the desired Favorskii product **9a** which was dehalogenated with lithium *t*-butyl alcohol to give acid **6**. The latter was converted into the aminomethyl derivative **13**, into the amine **14**, and into the parent hydrocarbon, homocubane (**17**). When ketone **7** was heated either with an aqueous solution of potassium hydroxide or with solid potassium hydroxide in benzene, acid **8a** was essentially the sole product. Nmr double resonance studies were carried out on ester **8b**.

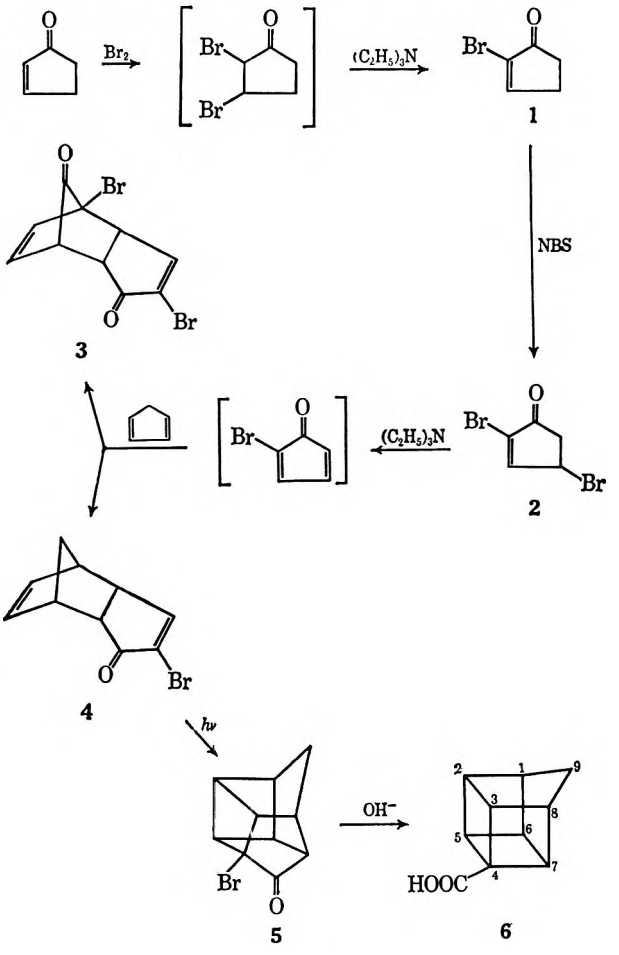
During an investigation of the biological activity of a variety of cage compounds it became necessary to devise a synthesis of monosubstituted pentacyclo-[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonanes. Soon after we began our work Scherer and coworkers[2] reported the synthesis of a polychlorinated compound containing this skeleton, for which they suggested the trivial name "homocubane." Since then several reports[3a–i] have described the synthesis and reactions of various substituted homocubanes. We wish to report now the results of our investigations on the synthesis of the parent hydrocarbon, homocubane,[4] and some of its monosubstituted derivatives.

Favorskii-type ring contraction of an appropriate halopentacyclodecanone has been used successfully to generate homocubane carboxylic acids containing halogen atoms and other functional groups.[3a,b] Since the requisite halopentacyclodecanones are conveniently prepared by photochemical cyclization of a Diels–Alder adduct, whose *endo* stereochemistry positions two carbon–carbon double bonds close enough together to allow internal cyclization to take place, we used this approach in two similar synthetic schemes.

The first sequence was based upon the fact that cyclopentadiene reacts with cyclopentadienone in a Diels–Alder reaction to give *endo*-dicyclopentadien-1-one.[5,6] By using an α-halocyclopentadienone[7] in this type of reaction we obtained α-bromo ketone **4**, which was ultimately transformed into homocubane-4-carboxylic acid (**6**) (Scheme I).

Our second route to the homocubanes (Scheme II) utilized polyhalopentacyclodecanones, which are readily prepared[8–10] from the stable tetrachlorocyclopentadienone ketals. The known tetrachloro ketone **7**, first prepared by Yates and Eaton,[9] provided a convenient starting point. The intermediate polyhalohomocubanes obtained by this sequence may then be dehalogenated to give the required product.

SCHEME I



Of the two approaches, the pathway outlined in Scheme I was the more satisfactory. Bromo ketone **1** was prepared by bromination of 2-cyclopentenone followed by dehydrobromination of the intermediate 2,3-dibromocyclopentanone with triethylamine. The

(1) A preliminary communication describing a portion of this work has appeared: G. L. Dunn, V. J. DiPasquo, and J. R. E. Hoover, *Tetrahedron Lett.*, 3737 (1966).

(2) K. V. Scherer, Jr., R. S. Lunt, III, and G. A. Ungefug, Abstracts, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, p 23N.

(3) (a) P. E. Eaton and T. W. Cole, Jr., *J. Amer. Chem. Soc.*, **86**, 3157 (1964); (b) K. V. Scherer, Jr., R. S. Lunt, III, and G. A. Ungefug, *Tetrahedron Lett.*, 1199 (1965); (c) K. V. Scherer, Jr., G. A. Ungefug, and R. S. Lunt, III, *J. Amer. Chem. Soc.*, **88**, 2859 (1966); (d) K. V. Scherer, Jr., and R. S. Lunt, III, *ibid.*, **88**, 2860 (1966); (e) W. G. Dauben and D. L. Whalen, *Tetrahedron Lett.*, 3743 (1966); (f) W. G. Dauben and D. L. Whalen, *J. Amer. Chem. Soc.*, **88**, 4739 (1966); (g) C. G. Chin, H. W. Cuts, and S. Masamune, *Chem. Commun.*, 880 (1966); (h) P. von R. Schleyer, J. J. Harper, G. L. Dunn, V. J. DiPasquo, and J. R. E. Hoover, *J. Amer. Chem. Soc.*, **89**, 698 (1967); (i) G. C. Barborak and R. Pettit, *ibid.*, **89**, 3080 (1967).

(4) Dauben and Whalen (see ref 3e) also have synthesized homocubane, but by an entirely different route.

(5) K. Hafner and K. Goliasch, *Ber.*, **94**, 2909 (1961).

(6) C. H. DePuy, M. Isaks, K. L. Eilers, and G. F. Morris, *J. Org. Chem.*, **29**, 3503 (1964).

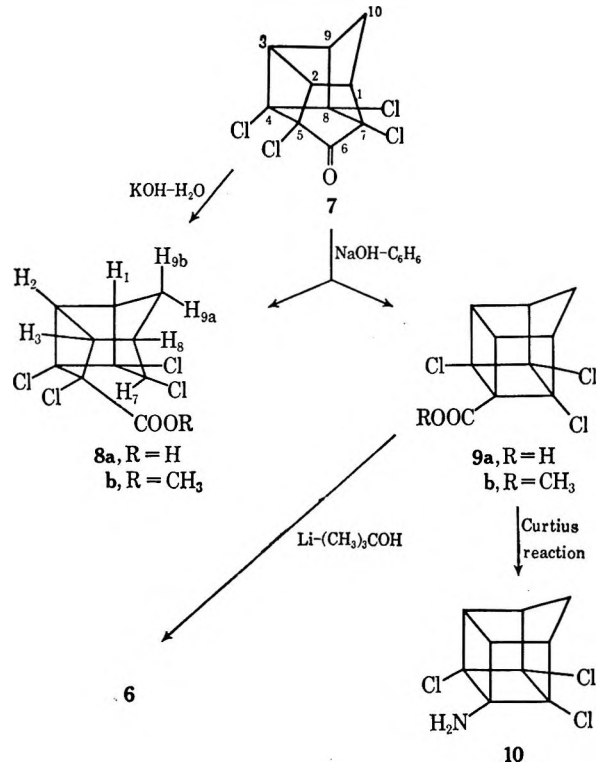
(7) P. E. Eaton and T. W. Cole, Jr., *J. Amer. Chem. Soc.*, **86**, 962 (1964).

(8) P. E. Eaton, Ph.D Dissertation, Harvard University, Cambridge, Mass., 1960.

(9) P. Yates and P. Eaton, *Tetrahedron*, **12**, 13 (1961).

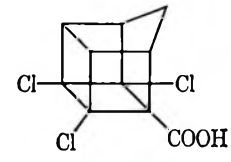
(10) G. W. Griffin and A. K. Price, *J. Org. Chem.*, **29**, 3192 (1964).

SCHEME II



structure of **1** is supported by its ultraviolet spectrum which shows a bathochromic shift[11] of 20 mμ from the absorption peak of 2-cyclopentenone and by the appearance of a single vinylic proton in its nmr spectrum.[12] Allylic bromination of **1** with N-bromosuccinimide gave dibromoenone **2** in good yield. Dehydrohalogenation of **2** with triethylamine at low temperature generated the extremely reactive 2-bromocyclopentadienone which immediately condensed with the cyclopentadiene present in the reaction mixture to form the Diels–Alder adduct **4** in low yield.[13] The expected *endo* stereochemistry[14] of **4** was confirmed by its ready photochemical cyclization to **5**. When **5** was treated with hot aqueous alkali, acid **6** was obtained in almost quantitative yield. The nmr spectrum of **6** shows a singlet[15] (δ 1.72) for the bridge methylene which would be expected for its symmetrical structure.

In the alternate route to homocubanes (Scheme II), tetrachloro ketone **7**, when heated with solid sodium hydroxide in boiling benzene, gave a mixture of three acids shown by glpc to be present in the ratio 11:8:1. The two major components[16] were separated by Florisil column chromatography of their methyl esters. The ester present in larger quantity (55%) was hydrolyzed to give a tetrachloro acid (**8a**) (see discussion below). The second major ester component (**9b**) was shown to be the product of a Favorskii-type ring contraction from analytical and spectral information. Since the ring contraction of **7** can proceed in either of two directions, the parent acid of ester **9b**, shown by glpc on several columns to be a single compound, may have structure **9a** or **11**. It has been assigned structure **9a**

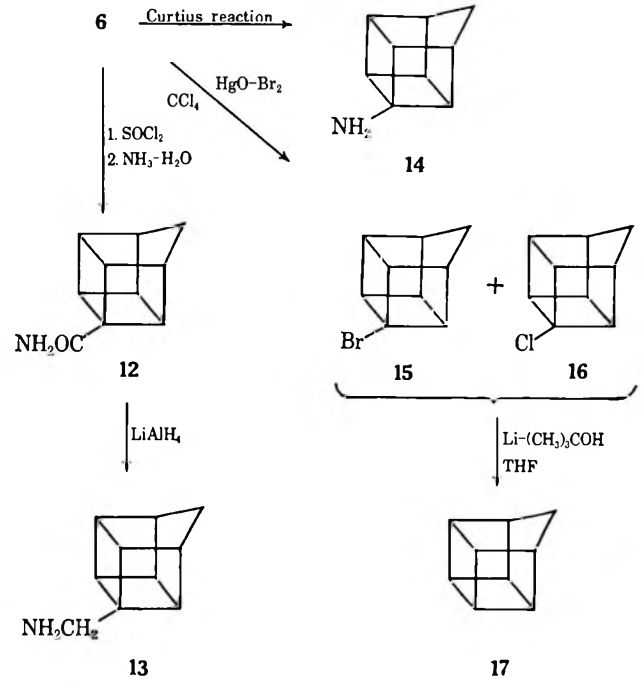


11

on the basis of the following evidence. When this acid was dechlorinated with lithium *t*-butyl alcohol, a semisolid acidic product was obtained which was homogeneous by glpc though its nmr spectrum indicated the presence of some olefinic acid, presumably a result of ring fission. The mixture was treated with bromine, a gummy precipitate was removed, and the residue was subjected to repeated fractional sublimation. A small sample of a pure acid was obtained and was shown by comparison of physical and spectral properties to be identical with homocubane-4-carboxylic acid (**6**) obtained earlier (Scheme I).

Acid **6** was converted (Scheme III) into the aminomethyl derivative **13** by lithium aluminum hydride reduction of amide **12**. Amine **14** was obtained from **6** *via* a Curtius reaction. When **6** was subjected to a Hunsdiecker reaction (Cristol modification)[17] in carbon

SCHEME III



tetrachloride the glpc of the product showed it to be a 1:1 mixture of two components. Although the components were not separated and individually identified it seems likely that they were 4-bromohomocubane (**15**) and 4-chlorohomocubane (**16**). The chloro compound **16** could have been formed by attack of the 4-

(11) L. F. Fieser and M. Fieser, *Steroids*, 19 (1959).

(12) C. H. DePuy, C. E. Lyons, and L. B. Rodewald [*J. Chem. Eng. Data*, **11**, 102 (1966)] reported that the nmr spectrum of 2-cyclopentenone showed a β-vinylic proton at δ 7.63 (sextet) and an α-vinylic proton at 6.11 (sextet). Compound **1** shows a triplet at δ 7.86 which is the expected pattern based on DePuy's results.

(13) The low yield encountered in this step apparently is due to the formation of a by-product which we assume has structure **3** since the infrared spectrum of the crude reaction product showed carbonyl absorption at 5.50 μ (see ref 7) in addition to the peaks at 5.88 and 6.35 μ expected for **4**.

(14) See J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961), for a review of the stereochemistry of the Diels–Alder reaction.

(15) The half-height width of the methylene peak is 2.5 Hz compared to 1 Hz for TMS. Any coupling between the bridge methylene protons and the adjacent bridgehead methines is therefore probably less than 1 Hz.

(16) The minor acid component (5%) remains unidentified.

(17) S. J. Cristol and W. C. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961).

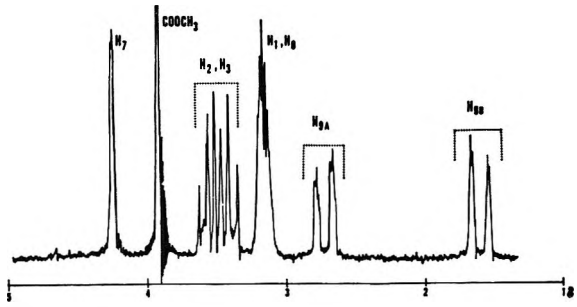


Figure 1.—Nmr spectrum (100 MHz) of tetrachloro ester **8b** in $CDCl_3$.

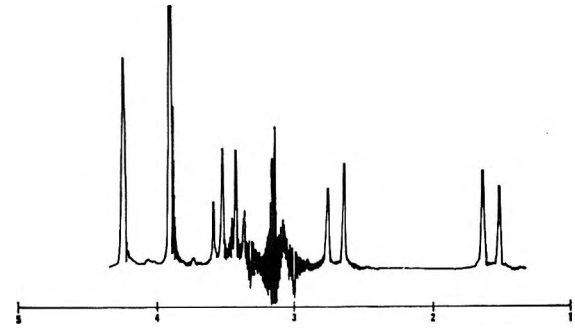
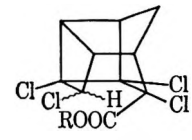


Figure 2.—Nmr spectrum of **8b** with irradiation of the H_1, H_8 peak.

homocubyl radical on the solvent (CCl_4).[18] Indirect support for this assumption follows from the lithium *t*-butyl alcohol dehalogenation of the mixture. Glpc of the reaction product after dehalogenation showed a single component which was isolated in low yield and shown to be pentacyclo[4.3.0.$0^{2,5}$.$0^{3,8}$.$0^{4,7}$]nonane (**17**), homocubane. This hydrocarbon, a very volatile solid, showed a simple infrared spectrum with no significant absorption between 3.6 and 7.3 μ. Its nmr spectrum was identical with that reported by Dauben,[3e] though our melting point was slightly higher.

The formation of **9a** as the only product of Favorskii ring contraction of **7** was rather surprising, though Scherer and coworkers[19] have reported a similar result with a ketone closely related to **7**. Examination of a molecular model of **7** shows that the C-5 chlorine is almost eclipsed with the C-2 hydrogen giving rise to some torsional strain and nonbonding interaction. However, the C-7 chlorine is conformationally *skewed* with respect to the C-1 hydrogen and apparently has no nonbonded interactions as severe as that shown by the C-5 chlorine. It is possible then, that the torsional[20] and nonbonded strains on the C-5 chlorine may be relieved as the ring contraction proceeds, with gradual lengthening of C-5 carbon–chlorine bond and with angle change, thus favoring formation of **9a** over **11**.

The tetrachloro acid, obtained as a major by-product from the reaction of ketone **7** with solid sodium hydroxide in boiling benzene, also was obtained almost exclusively (94%) when **7** was heated either in aqueous alkali or in benzene containing solid potassium hydroxide.[21] Elemental analysis (see the Experimental Section) and the nmr spectrum of its methyl ester, which showed a 1 H singlet at δ 4.27 indicative of a proton in a –CHCl grouping, indicated that this acid was a product of Haller–Bauer cleavage of ketone **7** and therefore must have structure **8** or **18**.

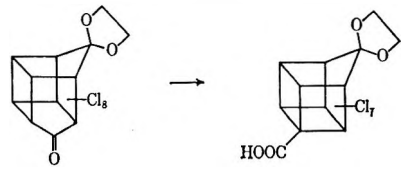


18a, R = H
b, R = CH_3

Scherer and coworkers[22] have shown that Haller–Bauer ring cleavage of octachlorohomocubanone proceeds with over-all retention of configuration; *i.e.*, both the carboxyl group and the proton are inside the cage. By analogy we have depicted the two alternatives, **8** and **18**, as the products resulting from ring cleavage with retention of configuration. Double resonance studies of ester **8b** (or **18b**) were carried out at 100 MHz[23] to determine the direction of ring opening. The 100-MHz nmr spectrum of **8b** (or **18b**) is shown in Figure 1. The additional multiplicity in the H-9a, H-9b doublets at δ 1.58 (1 H) and at 2.71 (1 H)[24] and the H-7 peak at δ 4.27 (1 H, –CHCl) in **8b** indicated the presence of weak spin–spin coupling. The spectrum also shows a sextet at δ 3.6–3.3 (2 H) and a broad peak at 3.25–3.05 (2 H). Irradiation of the δ 3.25–3.05 peak (Figure 2) caused the two upfield doublets and the downfield singlet to sharpen considerably, while the sextet collapsed to an AB quartet (J_{AB} = 7 Hz). Irradiation of the δ 3.6–3.3 sextet produced no observable change in the two upfield doublets or the downfield singlet. Irradiation of the δ 4.27 peak caused a slight change in the δ 3.25–3.05 peak only. These results are readily interpreted in terms of the structure shown above for **8b** with the assignments indicated on the spectrum (Figure 1), but not for the alternate structure **18b**. If the structure were **18**, irradiation of the bridge-

(18) F. W. Baker, H. D. Holtz, and L. M. Stock [*J. Org. Chem.*, **28**, 514 (1963)] have shown that brominative decarboxylation of bicyclo[2.2.2]-octane-1-carboxylic acid under the conditions suggested by Cristol in carbon tetrachloride leads to a mixture of the 1-chloro (68%) and 1-bromo (32%) derivatives. These authors suggest that the chloro derivative may be formed by attack of the 1-bicyclo[2.2.2]octyl radical on carbon tetrachloride.

(19) These investigators (see ref 3b) showed that ii was the exclusive product of ring contraction of i. In this case the exclusiveness was attributed



to the presence of a severe nonbonding interaction in i between the C-7 chlorine and an oxygen of the ketal which could be relieved upon going to ii but not to its isomer.

(20) Schleyer [*J. Amer. Chem. Soc.*, **89**, 701 (1967)] has discussed recently the importance of considering torsional effects in the stereochemistry of attack and departure in norbornane derivatives.

(21) G. W. Kenner, M. J. T. Robinson, C. M. B. Tylor, and B. R. Webster [*J. Chem. Soc.*, 1756 (1962)] obtained different products when sodium hydroxide was substituted for potassium hydroxide in a study of the Haller–Bauer cleavage of fluorenone.

(22) K. V. Scherer, Jr., G. A. Ungefug, and M. G. Ly, Abstracts, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p O9. The X-ray data reported at this meeting indicated that the configuration of the ring cleaved acid was opposite to that first postulated by these workers (see ref 3b).

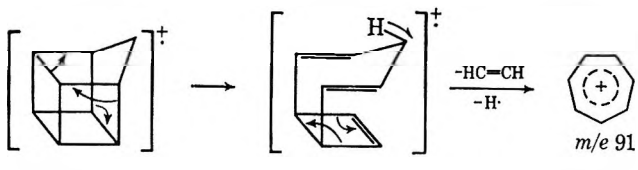
(23) We are grateful to Japan Electron Optics Laboratory, Medford, Mass., for performing the double resonance experiments.

(24) The low field doublet (δ 2.71) has been tentatively assigned to the methylene proton (H-9a) *syn* to the C-6, C-7 chlorines. The nmr spectra of some dihalonorbornenes [P. M. Subramanian, M. T. Emerson, and N. A. LeBel, *J. Org. Chem.*, **30**, 2624 (1965)] showed a large downfield displacement of the bridge methylene proton *syn* to *exo* halogens.

head protons H-1, H-8 should have shown that they are coupled only to the bridge methylene and H-2, H-3 protons and not to the -CHCl proton. We have considered only vicinal coupling to be important in the appearance of the spectrum. Though some small long range coupling between H-7 and H-9b might be expected and indeed might exist we have no real evidence to support it here.

The nmr spectrum of bromo ketone **5** showed a multiplet (1 H) at $\delta \backsim 2.4$, about 0.5 ppm upfield from the closest methine resonance. We have assigned this peak to proton 7 and in our preliminary communication we discussed in some detail our reasons for favoring this assignment. We noted also that this peak was about 0.13–0.15 ppm upfield from the methine signals of the parent hydrocarbon. Tetrachloro ketone **7** shows no upfield methine signals. This apparently anomalous behavior of protons α to a carbonyl in caged systems also has been noted by Stedman and coworkers.[25]

The mass spectrum of homocubane (**17**) shows a low intensity molecular ion peak of relative abundance (RA) 13 at *m/e* 118 and a base peak (RA, 100) at *m/e* 117, corresponding to loss of one hydrogen. The second most intense peak (RA, 39) in the spectrum was at *m/e* 91 which might be attributed to the tropylium ion, generated from **17** by loss of a hydrogen and



acetylene. The mass spectra of other cage systems, both structurally similar with[26] and structurally different from[27] homocubane also have shown a significant peak at *m/e* 91 suggestive of a tropylium ion. The spectrum of homocubane contains almost all the peaks shown in the mass spectrum of cycloheptatriene, which has been postulated to dissociate to the tropylium ion on electron impact.[28]

Experimental Section[29]

2-Bromo-2-cyclopentenone (1).—A solution of bromine (160 g, 1 mol) in CCl_4 (500 ml) was added dropwise during 45 min to a cold (0°) solution of 2-cyclopentenone (82 g, 1 mol) in CCl_4 (500 ml). After stirring 5 min at 0° a solution of triethylamine (210 ml, 151 g, 1.5 mol) in CCl_4 (500 ml) was added dropwise during 45 min while maintaining the temperature at 0°. When the addition was complete, the mixture was stirred at room temperature for 2 hr, then the precipitated triethylammonium bromide was filtered and washed well with CCl_4. The combined filtrate and washings were extracted with dilute HCl and with water and then dried. The solvent was removed at 40° *in vacuo* and the residue was distilled to give 82 g of 2-bromo-2-cyclopentenone (**1**), bp 52–56° (0.3 mm), which solidified in the receiver. One recrystallization from ether–hexane gave 68 g (42%) of **1** as colorless plates: mp 39–39.5°; ultraviolet maximum at 238 mμ (ϵ 8470); infrared absorption at 5.91 (C=O) and 6.32 μ (C=C); and nmr peaks at δ 7.86 (1 H triplet, J = 3 Hz) and at 2.88–2.43 (4 H multiplet).

Anal. Calcd for C_5H_5BrO: C, 37.30; H, 3.13; Br, 49.63. Found: C, 37.31; H, 3.11; Br, 49.32.

***endo*-2-Bromo-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (4).**—A mixture consisting of 2-bromo-2-cyclopentenone (**1**) (80 g, 0.50 mol), N-bromosuccinimide (98 g, 0.55 mol), azobisisobutyronitrile (ABIN) (2.5 g), and 1 l. of CCl_4 was heated at reflux. Additional 1-g portions of ABIN were added after 3 and 7 hr and then reflux was continued for a total of 24 hr.[30] The mixture was cooled to room temperature, and the succinimide was filtered and washed with CCl_4. The combined filtrate and washings were extracted with 5% aqueous $NaHCO_3$ solution and with water and then dried. The solvent was evaporated at 25° *in vacuo* to give 118 g of crude 2,4-dibromo-2-cyclopentenone (**2**)[31] as a dark liquid.

A solution of the dibromoenone **2** (118 g) in anhydrous ethyl ether (2 l.) was added dropwise during 2 hr to a solution of freshly distilled cyclopentadiene (570 ml) and triethylamine (145 ml, 105 g, 1.04 mol) in anhydrous ether (1 l.) cooled to −10°. The temperature was maintained between −10 and 0° during addition. The mixture was stirred for 15 min, the precipitated triethylammonium bromide (75 g, 82%) was collected and washed with ether. The combined filtrate and washings were extracted with dilute HCl, water, 5% aqueous $NaHCO_3$, and water and then dried. Evaporation of the ether *in vacuo* gave 137 g of residual oil. Thin layer chromatography on silica gel G with benzene showed four components. The residue was dissolved in hexane (900 ml), decanted from some insoluble gum and chromatographed on neutral alumina (6 lbs, Woelm, activity grade I). Elution with hexane (12 l.) gave some dicyclopentadiene; elution with benzene (32 l.) gave 31 g of 2-bromo-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (**4**); elution with 1:1 benzene–chloroform (10 l.) gave another 5 g of **4**. Further elution with benzene–chloroform or chloroform gave mixtures of desired product and what we presume to be 2,4-dibromo-3a,4,7,7a-tetrahydro-4,7-methanoinden-1,8-dione (**3**) based on a strong peak at 5.50 μ in its infrared spectrum.

The combined solids from the benzene and 1:1 benzene–chloroform eluates (36 g) were recrystallized from petroleum ether (30–60°) to give 32.8 g (29%) of **4**: mp 56–57°; ultraviolet maximum at 246 mμ (ϵ 6000); infrared absorption at 5.75 (C=O) and 6.27 μ (C=C); and nmr peaks at δ 7.56 (1 H doublet, J = 2.8 Hz), at 3.52–3.18 (2 H multiplet), at 3.18–2.75 (2 H multiplet), and at 1.71 (2 H complex triplet).

Anal. Calcd for $C_{10}H_9BrO$: C, 53.36; H, 4.03; Br, 35.50. Found: C, 53.38; H, 4.03; Br, 35.87.

5-Bromopentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (5).—A solution of ketone **4** (24 g, 0.103 mol) in ethyl acetate (1 l.) was irradiated with a 450-W Hanovia medium pressure mercury vapor lamp for 32 hr in a Pyrex immersion photolysis apparatus. The solvent was removed *in vacuo* and the dark residue was heated with boiling petroleum ether (400 ml). A small amount of insoluble dark solid was removed by filtration; the filtrate was treated with Darco and then cooled in a freezer. The desired product **5** was collected as colorless crystals (19 g, 79%): mp 39–40°; ultraviolet spectrum showed end absorption only; infrared absorption at 5.56 (m), 5.60 (sh), 5.63 (s), 5.67 (s), and 5.70 (s) μ (C=O);[32] and nmr peaks at δ 3.68–2.72 (6 H

(25) R. J. Stedman and L. S. Miller, *J. Org. Chem.*, **32**, 35 (1967); R. J. Stedman, private communication, Smith Kline and French Laboratories, Philadelphia, Pa., 1967.

(26) (a) W. L. Dilling, H. P. Braendlin, and E. T. McBee, *Tetrahedron*, **23**, 1211 (1967); (b) W. L. Dilling and M. L. Dilling, *ibid.*, **23**, 1225 (1967).

(27) (a) R. C. Fort, Jr., and P. von R. Schleyer, *Chem. Rev.*, **64**, 286 (1964); (b) C. Cupas, P. von R. Schleyer, and D. J. Trecker, Jr., *J. Amer. Chem. Soc.*, **87**, 917 (1965).

(28) S. Meyerson, J. D. McCollum, and P. N. Rylander, *ibid.*, **83**, 1401 (1961).

(29) Melting points were determined in open capillary tubes using a Thomas–Hoover Unimelt apparatus and are corrected. Ultraviolet spectra were determined in 95% ethanol using a Cary Model 14 recording spectrophotometer. Infrared spectra, unless indicated otherwise, were obtained in Nujol mull using a Perkin-Elmer Infracord; infrared spectra in solution were determined on a Perkin-Elmer Model 521 grating spectrophotometer. Nmr spectra were obtained in deuteriochloroform solution (unless indicated otherwise) on a Varian A-60 spectrophotometer using TMS as internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-D spectrometer operated by Morgan-Schaffer Corp., Montreal, Canada. Glpc were performed on an F & M Model 700 gas chromatograph equipped with a thermal conductivity detector. All solvents used in anhydrous reactions were dried over Linde 4A Molecular Sieve. Tetrahydrofuran was dried over a mixture of 4A and 13X sieves. Magnesium sulfate was used as drying agent for organic extracts.

(30) Tlc of the reaction after 1 hr showed the presence of unreacted starting compound **1**. The above conditions were necessary to force the reaction to completion.

(31) Because **2** tended to polymerize on distillation it was used in the next step without purification.

(32) Similar carbonyl multiplicity has been noted in other caged ketones and has been attributed to combination bands and/or Fermi resonance: P. E. Eaton and T. W. Cole, Jr., *J. Amer. Chem. Soc.*, **86**, 3157 (1964); P. E. Eaton and T. W. Cole, Jr., *ibid.*, **86**, 962 (1964).

multiplet) at ~2.4 (1 H multiplet), and an AB pattern centered at δ 1.79 (broad singlet with $w^1/_2$ = 3 Hz,[33] J_{AB} ~ 11 Hz).

Anal. Calcd for $C_{10}H_9BrO$: C, 53.36; H, 4.03; Br, 35.50. Found: C, 53.18; H, 4.05; Br, 35.19.

Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic Acid (6).—A solution of ketone **5** (21 g, 0.093 mol) in hot 30% aqueous KOH (350 ml) was heated at reflux for 4 hr. After cooling to room temperature, the solution was extracted with ether and then acidified with dilute HCl. The mixture was extracted with ether, the combined extracts were dried, treated with Darco, and then evaporated *in vacuo* to give 15 g (99%) of **6**, mp 92–93°. A sample (600 mg) was further purified by vacuum sublimation at 80–90° (1 mm) to give 500 mg of the acid: mp 93–95°; infrared absorption at 5.96 μ (acid C=O); and nmr peaks at δ 11.45 (1 H singlet, COOH), at 3.72–3.05 (7 H multiplet), and at 1.72 (2 H singlet).

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.12; H, 6.17.

4,5,7,8-Tetrachloropentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (7).[34]— A solution of 2,3,3a,7a-tetrachloro-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-one (10 g, 0.035 mol) in 400 ml of ethyl acetate was irradiated for 1.5 hr with a 450-W Hanovia mercury vapor lamp in a quartz immersion photolysis apparatus. The solvent was evaporated by heating *in vacuo* to give 9.7 g of crude solid which was sublimed at 90–120° (1 mm) to give 7.9 g (79%) of ketone **13**: mp 113–115° (lit.[34] 113.5–114.5°); infrared absorption (CH_2Cl_2) at 5.52 μ (C=O); and nmr peaks at δ 3.91–2.96 (4 H multiplet) and an AB quartet with A at 2.54 and B at 1.91 (J_{AB} = 13 Hz).

Reaction of 4,5,7,8-Tetrachloropentacyclo[5.3.0.0^{2,5}.0^{3,9}0^{4,8}]-decan-6-one (7) with NaOH in Benzene.—Ketone **7** (14.2 g, 0.05 mol) was added in one portion to a stirred suspension of powdered NaOH (10 g, 0.25 mol) in 1125 ml of benzene and the mixture was heated at reflux under a Dean–Stark trap overnight. After cooling to room temperature 500 ml of water was added and the mixture was agitated vigorously for a few minutes. The dark aqueous layer was separated, the benzene layer was washed with water, and the washings were combined with the original aqueous layer. Two methods of isolation were used.

Method A.—The aqueous solution was cooled (5–10°) and the pH was adjusted to 5–7 with concentrated HCl. Using a pH meter (Beckman Zeromatic) the solution was carefully adjusted to pH 3.5 by dropwise addition of 2 *N* HCl. If the pH drifted above 3.65 it was readjusted to 3.5. When the pH no longer rose above 3.65 (after 30 min) the precipitated solid was collected to give 3.5 g (26%) of **5,6,7-trichloropentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxylic acid (9a)**, mp 212–214°. One recrystallization from aqueous methanol gave colorless prisms: mp 214–216°; infrared absorption at 5.90 μ (acid C=O); and nmr peaks (DMSO-d_6) at δ 3.70–3.34 (4 H multiplet) and an AB quartet with A at 2.14 and B at 1.80 (J_{AB} = 13.5 Hz).

Anal. Calcd for $C_{10}H_7Cl_3O_2$: C, 45.23; H, 2.66; Cl, 40.06; neut equiv, 265. Found: C, 45.13; H, 2.89; Cl, 40.39; neut equiv, 265.

Acidification of the filtrate to pH <0.5 gave 10 g of acidic product which was shown by glpc,[35] after treatment with ethereal diazomethane, to consist of 8% closed acid **9a** and 92% open acid **8a**.

Method B.—Alternatively, the aqueous layer was acidified to a pH <0.5 with concentrated HCl and extracted with ether to give a mixture of acids. In a typical experiment 40 g of tetrachloro ketone **7** gave 33 g of crude acid mixture. A portion of the mixture (31 g) was esterified with ethereal diazomethane.[36] The esters were separated by column chromatography on Florisil (1 kg). Elution with 1:3 benzene–hexane gave 16 g (38%) of ester **8b**: mp 134–135°; infrared absorption at 5.76 μ (ester C=O); and nmr peaks at δ 4.27 (1 H broad singlet), at 3.90 (3 H singlet), at 3.6–3.28 (2 H multiplet), at 3.28–3.02 (2 H multiplet), and an AB quartet with A at 2.71 and B at 1.58 (J_{AB} = 12 Hz).

Anal. Calcd for $C_{11}H_{10}Cl_4O_2$: C, 41.81; H, 3.19; Cl, 44.88. Found: C, 41.86; H, 3.19; Cl, 44.60.

Elution with 1:1 benzene–hexane gave 8.7 g (24%) of ester **9b**, mp 62–63°. Sublimation at 50° under high vacuum raised the melting point to 63–64°. An infrared absorption peak was located at 5.80 μ (C=O ester); and nmr peaks were at δ 3.82 (-OCH_3, singlet) and 4.10–3.42 (multiplet, 7 H) with an AB quartet having A at 2.34 and B at 1.83 (J_{AB} = 13 Hz).

Anal. Calcd for $C_{11}H_9Cl_3O_2$: C, 47.26; H, 3.24; Cl, 38.05. Found: C, 47.26; H, 3.30; Cl, 38.22.

4,5,6,7-Tetrachlorotetracyclo[4.3.0.0^{2,5}.0^{3,8}]nonane-4-carboxylic Acid (8a).—A solution of ketone **7** (1.0 g, 3.5 mmol) in a mixture of 30% aqueous KOH (20 ml) and dioxane (7.5 ml) was heated at reflux for 4 hr. The mixture was cooled and extracted with ether. The aqueous layer was then acidified with concentrated HCl, extracted with ether and the combined extracts were washed with water and dried. The tan solid remaining after evaporation of the solvent was dissolved in ether, the solution was filtered to remove a small amount of insoluble material and then the filtrate was evaporated *in vacuo* to give 1 g (94%) of off-white solid, mp 212–215°.

A portion of the acid was esterified with ethereal diazomethane and analyzed by glpc on a 6-ft column of 5% SE-30 at 200°. The chromatogram showed 2% of an unknown component, 4% of ester **9b**, and 94% of ester **8b**.

Two recrystallizations from methanol–water gave colorless crystals, mp 214–216°. Glpc[33] of an esterified sample showed 100% **8a**; an infrared absorption peak appeared at 5.81 μ (C=O, acid), and nmr peaks (pyridine) were at δ 5.29 (1 H broad singlet), at 3.70–3.48 (2 H multiplet), and at 3.48–3.01 (2 H multiplet) with an AB quartet having A at 2.62 and B at 1.46 (J_{AB} = 12 Hz).

Anal. Calcd for $C_{10}H_8Cl_4O_2$: C, 39.77; H, 2.67; Cl, 46.96; neut equiv, 302. Found: C, 40.03; H, 2.81; Cl, 47.13; neut equiv, 298.

The acid also was prepared by alkaline hydrolysis of ester **8b** obtained in method B above. Samples of the acid obtained from the two routes were shown to be identical upon comparing their physical and spectral properties.

4-Amino-5,6,7-trichloropentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (10).—A solution of acid **9a** (5.0 g, 0.019 mol) in 75 ml of thionyl chloride was heated at reflux for 2.5 hr, the solution was evaporated *in vacuo*, the residue was taken up in benzene and evaporated again to give 5.1 g of solid acid chloride. This was taken up in 160 ml of acetone, the solution was cooled in an ice bath, and then a solution of sodium azide (1.53 g, 0.024 mol) in 15 ml of water was added. After stirring in the cold for 15 min the mixture was diluted with 240 ml of water. The turbid mixture was extracted with ether and the combined dried extracts evaporated at 25° *in vacuo* to give 4.4 g of azide. The azide was dissolved in 35 ml of benzene and the solution heated at reflux for 1 hr. Removal of the solvent *in vacuo* yielded 3 g of isocyanate. A solution of the isocyanate in a mixture of tetrahydrofuran (120 ml) and concentrated HCl (30 ml) was heated at reflux for 1 hr and then heated *in vacuo* to remove the THF. The aqueous residue was diluted with water (75 ml), basified with 10% aqueous NaOH, and extracted with ether. Treatment of the dried ethereal solution with ethereal HCl precipitated 2.0 g (38%) of **10** hydrochloride. The hydrochloride was purified by recrystallization from ethanol–ether: mp 192–195° dec; nmr peaks (D_2O–DCl)[37] at δ 3.98–3.52 (4 H multiplet) and an AB quartet with A at 2.38 and B at 1.93 (J_{AB} = 13 Hz).

Anal. Calcd for $C_9H_9Cl_4N$: C, 39.60; H, 3.32; Cl, 51.95; N, 5.13. Found: C, 39.69; H, 3.24; Cl, 51.98; N, 5.15.

A sample of the free base **10** was prepared by basification of an aqueous solution of the hydrochloride, the precipitate was collected and recrystallized from hexane, mp 89–91° dec; infrared absorption ($CHCl_3$) appeared at 2.90 and 2.95 (-NH_2 stretching) and at 6.20 μ (-NH_2 bending).

Anal. Calcd for $C_9H_8Cl_3N$: C, 45.70; H, 3.41; Cl, 44.97; N, 5.92. Found: C, 45.69; H, 3.36; Cl, 45.17; N, 5.80.

Dechlorination of 5,6,7-Trichloropentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]-nonane-4-carboxylic Acid (9a).—To a solution of **9a** (10.6 g, 0.04 mol) in dry THF (200 ml) containing *t*-butyl alcohol (23 ml, 0.24 mol) was added finely cut pieces of lithium wire (3.3 g, 0.48 mol). Within a few minutes the mixture began to reflux spontaneously. As the reaction subsided (15 min) external heat was applied to maintain reflux for 15 min. A 12-ml quantity of *t*-butyl alcohol and 1.7 g of finely cut lithium wire were

(33) The half-height width ($w^1/_2$) of TMS was 1 Hz.

(34) We have used a modification of the procedure described by P. Yates and P. Eaton, *Tetrahedron*, **12**, 13 (1961).

(35) Gas chromatographic analyses were carried out at 190° on a 4-ft column of 10% SE-30 on Diatoport S.

(36) Glpc of the esterified mixture showed that it contained 5% unknown material, 40% ester **9b**, and 55% ester **8b**.

(37) 3-Trimethylsilyl-1-propanesulfonic acid sodium salt was used as internal standard.

added and the mixture was heated at reflux for 3 hr to complete the reaction. The mixture was cooled, poured into an ice–water mixture (1 l.) and after the excess lithium had decomposed the aqueous solution was extracted with ether. The aqueous layer was separated, acidified with concentrated HCl, and extracted with ether. The dried ether layer was evaporated *in vacuo* to give 5.2 g of a semisolid acid mixture. Although glpc showed a single peak, nmr data indicated the presence of unsaturation.

A portion of the acid mixture (1.8 g) was treated with bromine in carbon tetrachloride, the precipitated solid filtered and the filtrate evaporated. The filtrate residue (1.6 g) was twice recrystallized from petroleum ether to give 0.70 g of crude acid. Repeated fractional sublimation finally gave a pure sample of acid (40 mg), mp 91.5–93°. This acid was shown by spectral comparisons and mixture melting point to be identical with the homocubane-4-carboxylic acid (**6**), obtained by the alternate route (Scheme I).

Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-carboxamide (12).—A solution of acid **6** (5.0 g, 0.031 mol) in 25 ml of thionyl chloride was heated at reflux for 1 hr and then allowed to stand overnight at room temperature. The thionyl chloride was removed by heating *in vacuo*, the crude acid chloride was dissolved in 15 ml of THF and added dropwise (3 min) to 75 ml of cold concentrated NH_4OH. After stirring 1 hr, the mixture was diluted with 25 ml of water and the precipitate was collected, mp 261–263°. Recrystallization from 1:1 acetonitrile–isopropyl alcohol gave 3.8 g (76%) of off-white crystals: mp 261–263°; infrared absorption at 2.95, 3.10, 6.00, and 6.19 μ; and nmr peaks (CF_3-COOH) at δ 3.90–3.18 (7 H unsymmetrical doublet) and at 1.85 (2 H singlet).

Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.65; H, 7.06; N, 8.74.

Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane-4-methylamine (13) Hydrochloride.—Amide **12** (3.0 g, 0.0186 mol) was added portionwise (1 hr) under nitrogen to a slurry of lithium aluminum hydride (3.04 g, 0.08 mol) in 400 ml of hot THF. The reaction was heated at reflux for 46 hr, cooled in ice and the excess lithium aluminum hydride decomposed by cautious addition of water (4 ml) followed by a saturated aqueous Na_2SO_4 solution. The white suspension was filtered through a Celite pad and the filtrate evaporated to a small liquid residue *in vacuo*. The residue was dissolved in ether, a small amount of water was separated and then the dried organic solution was treated with ethereal HCl to give 1.5 g (44%) of **13** hydrochloride as a colorless solid. Recrystallization from 1:1 isopropyl alcohol–ethyl acetate gave 1.0 g of crystalline hydrochloride: mp >300°; infrared absorption at 6.20 (sh), 6.27, 6.36, 6.62 μ; and nmr peaks (D_2O–DCl) at δ 3.42–2.98 (9 H unsymmetrical doublet) and at 1.67 (2 H singlet).

Anal. Calcd for $C_{10}H_{14}ClN$: C, 65.39; H, 7.68; Cl, 19.30; N, 7.63. Found: C, 65.54; H, 7.65; Cl, 19.03; N, 7.54.

4-Aminopentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (14) Hydrochloride.—A solution of acid **6** (11.6 g, 0.072 mol) in thionyl chloride (50 ml) was allowed to stand for 18 hr at room temperature then heated at reflux for 1 hr. Excess thionyl chloride was removed *in vacuo* and the remaining liquid acid chloride was dissolved in acetone (60 ml), cooled to 0–5°, and treated with a solution of sodium azide (7.5 g) in water (75 ml). After stirring at 0–5° for 30 min the mixture was diluted with water (800 ml) and extracted with benzene, and the combined extracts were dried. The benzene solution was heated at reflux for 1 hr, the solvent was removed *in vacuo* and the residual isocyanate was heated in a refluxing mixture of tetrahydrofuran (500 ml) and concentrated HCl (120 ml). The solution was concentrated to 0.25 volume *in vacuo*, diluted with water (300 ml), and extracted with ether. The aqueous solution was basified with 10% aqueous NaOH solution and extracted with ether. The combined dry extracts were treated with excess ethereal HCl and the precipitate was collected (8 g). Recrystallization from isopropyl alcohol–ethyl acetate gave 5.3 g of **14** hydrochloride, mp 188–190° dec. The mother liquor yielded a second crop upon further cooling (1.5 g), mp 188–190° dec, to give a total of 6.8 g (56%); infrared absorption appeared at 6.29 and 6.39 μ; and nmr peaks (D_2O–DCl) were at δ 3.68–3.17 (7 H multiplet) and at 1.73 (2 H singlet).

Anal. Calcd for $C_9H_{12}ClN$: C, 63.72; H, 7.13; N, 8.26; Cl, 20.90. Found: C, 63.78; H, 7.19; N, 8.13; Cl, 20.71.

Pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (Homocubane) (17).—A solution of bromine (2.5 g, 0.0156 mol) in 25 ml of CCl_4 was added dropwise (1 hr) to a solution of acid **6** (2.50 g, 0.0152 mol) in 65 ml of boiling CCl_4 containing red mercuric oxide (2.50 g, 0.0115 mol). When addition was complete the mixture was heated at reflux for 2 hr, cooled to room temperature and then filtered. The filter cake was washed with CCl_4 and the combined filtrate and washings were extracted with five 25-ml portions of 10% aqueous NaOH. The dried ($CaSO_4$) organic solution was concentrated to ~2 ml, diluted with pentane, and then chromatographed on 75 g of neutral alumina (Woelm, activity grade I) in pentane. The initial pentane eluates gave 1.2 g of liquid as a mixture of 4-chloro- (**16**) and 4-bromohomocubane (**15**).[38]

A portion of the mixture (0.5 g) was dissolved in 15 ml of dry THF containing *t*-butyl alcohol (0.42 g, 5.7 mmol), then finely cut pieces of lithium wire (0.08 g, 11.4 mmol) were added. The mixture was heated at reflux for 1.5 hr, cooled to room temperature and poured onto 150 g of crushed ice. After the excess lithium had decomposed, the mixture was extracted with pentane. The combined dried pentane extracts were distilled until no further volatile distillate collected. The residue[39] was taken up in a few drops of warm methanol, then cooled in ice to give a colorless solid, 50 mg. A second crystallization from methanol gave **17** as a colorless, volatile solid: mp 107.5–108.5° (sealed capillary); infrared absorption peaks (CCl_4) at 3.41, 7.82, 8.01, 8.12, 8.42, 10.85, 11.24, and 11.42 μ; and nmr peaks at δ 3.40–3.00 (8 H unsymmetrical doublet) and at 1.69 (2 H singlet). The mass spectrum shows principal peaks at *m/e* 118, 117, 115, 103, 91, 78, 77, 65, 63, 53, 52, 51, 50, 39, and 27.

Anal. Calcd for C_9H_{10}: C, 91.47; H, 8.53. Found: C, 91.19; H, 8.47.

Registry No.—**1**, 10481-34-2; **4**, 10481-35-3; **5**, 15844-10-7; **6**, 15844-05-0; **8a**, 15892-95-2; **8b**, 15892-96-3; **9a**, 15892-97-4; **9b**, 15892-98-5; **10**, 15892-99-6; **10** HCl, 15893-00-2; **12**, 15844-06-1; **13** HCl, 15844-07-2; **14** HCl, 15844-09-4; **17**, 15844-08-3.

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(38) Glpc at 100° on a 6-ft column of 5% SE-30 on Chromosorb W showed that two components were present in a 1:1 ratio, with retention times of 5.6 and 9.0 min.

(39) Glpc of the residue under the conditions of ref 38 showed it to contain a single component of retention time 2.3 min along with some solvent.

Acid-Catalyzed Hydrolysis of 1-Arylcyclopropyl Acetates. Electrophilic Cyclopropane Ring Cleavage

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Eight 1-arylcyclopropyl acetates **5** were prepared and subjected to hydrolysis with 0.1 *N* hydrochloric acid in 50 wt % aqueous dioxane at 40, 55, and 70°. With the exception of the hydrolyses at 40° of those acetates substituted with electron-withdrawing groups, all compounds gave nonlinear first-order plots (production of acetic acid) which could be analyzed in terms of normal A'2 hydrolysis to cyclopropanol **6** in competition with ring opening to an unstable intermediate which breaks down to propiophenone **7**. The structure of the intermediate was tentatively assigned as hydroxyacetate **8** on the basis of the product study and rate meaurements on model compounds.

Although the acid-catalyzed opening of various substituted cyclopropanols is now well documented,[2,3] the extent to which such a reaction might intervene during the acidic hydrolysis of a simple cyclopropyl carboxylate has not been previously determined and should be of considerable interest. In view of the often quoted similarity between the cyclopropane ring and a double bond, it is of interest to note that the preferred path for acid hydrolysis of enol esters involves slow addition of water across the double bond followed by alkyl–oxygen cleavage,[4] a result which suggest that ring cleavage during the hydrolysis of cyclopropyl esters might be important.

In the following study eight 1-arylcyclopropyl acetates have been prepared and the rates of acid-catalyzed hydrolysis measured at several temperatures.

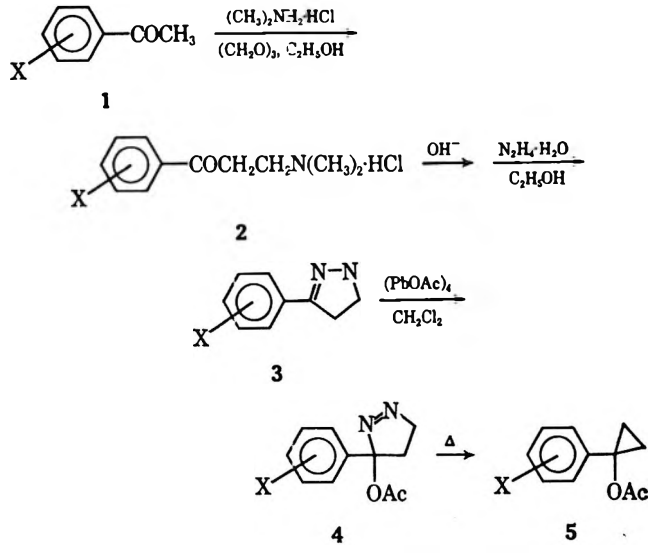
Results

All the cyclopropyl esters of general structure **5** were synthesized from the substituted acetophenones **1** according to the general procedure described by Freeman[5] and outlined in Scheme I.

Kinetic measurements of the hydrolyses of acetates **5** with *ca.* 0.1 *N* hydrochloric acid in 50 wt % aqueous dioxane were carried out at several temperatures by following the rate of production of acetic acid. At 40° all the substituted esters except acetates **5b** and **5c**, in which an electron donor is located in the *para* position, followed good pseudo-first-order kinetics (Table I). A simple extrathermodynamic relationship between log (relative rate) and the Hammett σ values was found and exhibited a slope of -0.108.[6,7]

Acetates **5b** and **5c** at 40, 55, and 70°, and all other acetates at temperatures above 40° (except **5e** at 55°) displayed non-first-order behavior as indicated in Figure 1 for the *p*-tolyl ester **5b** at 70°. A rational kinetic scheme capable of explaining these results consists of a direct hydrolysis path k_2, involving the normal acyl–oxygen cleavage step, in competition with a two-step sequence which results in initial cleavage of the

SCHEME I



a, X = H
b, X = *p*-CH_3
c, X = *p*-CH_3O
d, X = *m*-CH_3O
e, X = *m*-NO_2
f, X = *p*-Br
g, X = *p*-Cl
h, X = *m*-Br

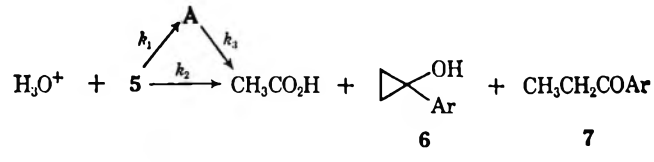
TABLE I

RATE DATA FOR THE ACID HYDROLYSES OF 1-ARYLCYCLOPROPYL ACETATES IN 50 WT % AQUEOUS DIOXANE[a] AT 40°

Substituent	No. of runs	$k(H^+) \times 10^5$ [b,c]	$k \times 10^5$ [b,d]	Rel rate
H (**5a**)	4	4.69	4.79	1.000
m-CH_3O (**5d**)	3	4.56	4.49	0.937
p-Cl (**5g**)	2	4.43	4.35	0.908
p-Br (**5f**)	3	4.41	4.33	0.904
m-Br (**5h**)	3	4.57	4.08	0.852
m-NO_2 (**5e**)	5	3.87	3.98	0.831
	4[e]	15.58[e]	15.53[e]	...

[a] *Ca.* 0.1 *N* in hydrochloric acid. [b] Average deviation for several runs is ±1% except for *m*-NO_2 (**5e**) for which it is ±1.5%. [c] Units of sec^{-1}. [d] Units of mol $l.^{-1}$ sec^{-1}. [e] 55°.

cyclopropane ring to intermediate A which undergoes hydrolysis. A similarity in the values for k_2 and k_3 re-



sults in the type of behavior indicated in Figure 1. Assumption that the three steps are essentially irreversible under the reaction conditions (see Discussion) and

(1) Taken from the Ph.D. Dissertation of W. L. B. Support of this work by a grant from the University of Kansas General Research Fund is gratefully acknowledged.

(2) (a) C. H. DePuy, F. W. Breitbeil, and K. P. DeBruin, *J. Amer. Chem. Soc.*, **88**, 3347 (1966); (b) C. H. DePuy and F. N. Breitbeil, *ibid.*, **85**, 2176 (1963).

(3) P. S. Wharton and T. I. Bair, *J. Org. Chem.*, **31**, 2480 (1966).

(4) J. A. Landgrebe, *ibid.*, **30**, 2997 (1965).

(5) (a) J. Freeman, *ibid.*, **28**, 885 (1963); (b) *ibid.*, **29**, 1379 (1964).

(6) The Hammett relationship for acid-catalyzed hydrolysis of benzyl acetates in 60% acetone in water at 40° has a ρ value of -0.053.[7]

(7) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).

solution of the appropriate differential equations leads to the following expression in which x is the fraction of reaction.

$$x = 1 + \frac{1}{k_1 + k_2 - k_3}[(k_3 - k_2)e^{-(k_1+k_2)t} - k_1e^{-k_3t}] \quad (1)$$

Values of k_1, k_2, and k_3 were chosen by a GE-625 computer so as to obtain the best possible fit of the equation to the actual plot of the raw data. The χ^2 function minimized by the computer was found to be rather sensitive to variations in k_2 and k_3 but insensitive to k_1; thus, values for k_2 and k_3 became constant after only 5–10 iterations while values for k_1 continued to fluctuate markedly even after 40 iterations. Computed values of k_2 and k_3 are listed in Table II.

TABLE II

COMPUTED RATE CONSTANTS FOR THE HYDROLYSES OF 1-ARYLCYCLOPROPYL ACETATES WITH 0.1 N HYDROCHLORIC ACID IN 50 WT % AQUEOUS DIOXANE

Substituent	No. of runs	Temp, °C	Second-order constants[a] $k_2 \times 10^4$	$k_3 \times 10^4$	Average deviation (±) $k_2 \times 10^4$	$k_3 \times 10^4$	Rel rates (70°) k_2	k_3
p-CH_3O (5c)	2	70	8.65	8.65	0.14	0.14	1.14	1.01
	2	55	4.60	4.48	0.19	0.32	...	...
p-CH_3 (5b)	2	70	7.90	7.90	0.12	0.12	1.04	1.01
	3	40	1.02	1.02	0.08	0.08	...	...
H (5a)	5	70	7.60	7.82	0.22	1.00	1.00	1.00
m-CH_3O (5d)	2	70	8.19	8.40	0.10	0.11	1.08	1.07
p-Cl (5g)	2	70	6.32	5.73	0.08	0.51	0.83	0.73
p-Br (5f)	5	70	7.43	7.92	0.33	0.62	0.98	1.01
m-Br (5h)	3	70	5.98	5.98	0.11	0.11	0.79	0.77
m-NO_2 (5e)	3	70	6.92	7.40	0.40	0.61	0.91	0.95

[a] Units of l. mol^{-1} sec^{-1}.

Although there is some scatter in a plot of log k_2 *vs.* Hammett σ for the data at 70°, the slope lies between the extreme limits of −0.06 and −0.24.

Activation parameters calculated for k_2 from the data in Tables I and II are listed in Table III.

TABLE III

ACTIVATION PARAMETERS FOR k_2[a]

Substituent	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
p-CH_3O (5c)	16.9	−23
p-CH_3 (5b)	13.9	−32
H (5a)	19.0	−18
m-CH_3O (5d)	20.0	−14
p-Cl (5g)	18.4	−19
p-Br (5f)	19.5	−16
m-Br (5h)	18.4	−19
m-NO_2 (5e)	19.7	−15

[a] Determined from data at 40 and 70° except for 5c for which data at 55 and 70° were used.

Products identified after partial hydrolysis of several 1-arylcyclopropyl acetates at two temperatures are listed in Table IV.

Discussion

The data of Table I clearly indicate that at 40° those 1-arylcyclopropyl acetates substituted with electron-withdrawing groups undergo hydrolysis in complete accord with the classical $A'2$ mechanism.[8] That electrophilic ring cleavage was unimportant under these circumstances was confirmed by the absence of propiophenone **7** among the products (Table IV).

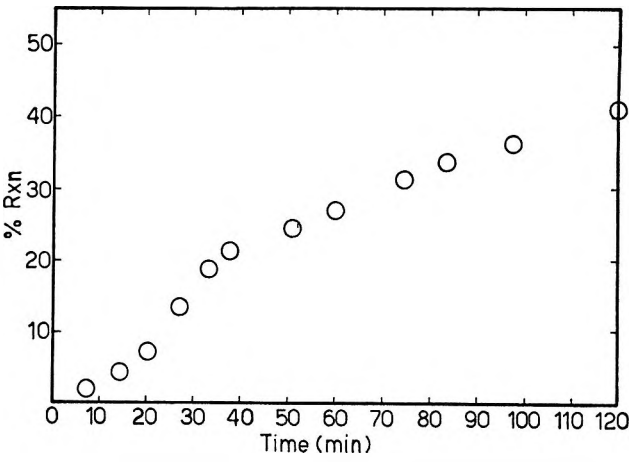


Figure 1.—Hydrolysis of 1-(*p*-tolyl)cyclopropyl acetate with 0.1 N hydrochloric acid in 50 wt % aqueous dioxane at 70°.

TABLE IV

PRODUCTS DETECTED AFTER ACID HYDROLYSIS OF 1-ARYLCYCLOPROPYL ACETATES IN 50 WT % AQUEOUS DIOXANE FOR 4.5 HALF-LIVES[a]

Substituent	Temp, °C	Nonlinear first-order plot	Cyclopropanol 6	Propiophenone 7
p-CH_3O (5c)	70	+	+	+
	40	+	+	+
H (5a)	70	+	+	+
	40	−	+	?
p-Cl (5g)	40	−	+	−
m-Br (5h)	70	+	+	+
m-NO_2 (5e)	40	−	+	−

[a] Residual starting material was detected in all experiments.

For acetates **5b** and **5c** in which an electron donor was present on the aromatic ring or for all esters at elevated temperatures, the kinetic behavior illustrated in Figure 1 was observed and could be analyzed by the scheme previously presented in which a dual path for the production of acetic acid was envoked. An important observation consistent with the propsed kinetic scheme was that only under circumstances which resulted in nonlinear first-order kinetics was the presence of ketone **7** noted among the products (Table IV).

Although the electrophilic opening of cyclopropanol **6** might conceivably account for the production of a portion of ketone **7**,[9–11] this process does not affect the rate of production of acetic acid and is therefore not directly related to the observation of unusual kinetic behavior. The proposed path k_1,k_2 not only accounts for the observed rate data but demands the presence of ketone **7** as a product.

The nature of intermediate A must be deduced indirectly since it does not accumulate under the reaction conditions. Acid-catalyzed opening of the ring of

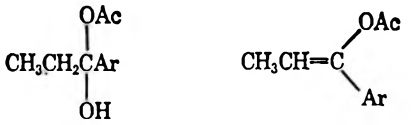
(8) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1963, p 319.

(9) Ring opening of 1-(*p*-tolyl)cyclopropanol with 5 N perchloric acid in 60:40 (v/v) dioxane–water at 50° occurs with a rate constant of 1.01 × 10^{-5} sec^{-1}.[10] Thus, it seems unlikely that under the conditions for the product study on **5b** at 40°, more than a small fraction of the propiophenone could have been accounted for by ring opening of the alcohol.

(10) R. A. Klein, Ph.D. Dissertation, Iowa State University, 1965.

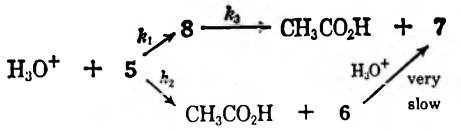
(11) 1-(*p*-Chlorophenyl)cyclopropanol and 1-(*p*-methoxyphenyl)cyclopropanol prepared from the corresponding acetates by reduction with lithium aluminum hydride, when subjected to hydrolysis under the conditions used in the product study, produced only a trace of the corresponding propiophenones.

acetate **5** with subsequent or simultaneous attack by water would result in the formation of hydroxyacetate **8**, or *via* an elimination reaction, enol acetate **9**. A



8 **9**

model enol acetate, 1-*p*-anisyl-1-acetoxypropene, was prepared from the corresponding ketone and found to undergo acid-catalyzed hydrolysis (55°) in aqueous dioxane with a rate constant one-fourth that of the k_3 hydrolysis constant of 1-(*p*-anisyl)cyclopropyl acetate under the same conditios. This result implies that intermediate A is probably the labile hydroxyacetate **8**.[12,13] The over-all kinetic scheme is summarized below.



It should be noted that the small relative rate range for the k_2 values is associated with a substantial compensation of activation enthalphy and entropy values (Table III).[14]

Experimental Section[15]

1-Arylcyclopropyl acetates (**5**) were prepared from the corresponding acetophenone *via* the Mannich reaction,[16] followed by neutralization of the resulting β-dimethylaminopropiophenone hydrochloride with 1 *N* sodium hydroxide, treatment of the crude amine with 90–100% hydrazine hydrate,[17] oxidation of the pyrazoline with lead tetraacetate,[5,18] and thermal decomposition to the cyclopropane.[5] The crude intermediate pyrazoline was isolated by crystallization and rapid filtration under nitrogen. Those 1-arylcyclopropyl acetates obtained as solids were crystallized from *n*-pentane.

It was noted that 3-*p*-anisyl-Δ^2-pyrazoline was quite air sensitive. Exposure to air resulted in a vigorous exothermic reaction.

If precautions were not taken to neutralize the hydrochloride of β-dimethylamino-*m*-nitropropiophenone with a layer of ether present, considerable polymeric material formed. The ether solution of free amine was used directly in the next step. Total polymerization could not be avoided during the neutralization of the hydrochloride of β-dimethylamino-*p*-nitropropiophenone consistent with observation by Knott[19] and Nobles and Burckhalter.[20]

(12) Newman and Smith,[13] having formed the carbonyl addition product of *n*-butylmagnesium bromide and acetic anhydride at −70°, were unable to isolate any hydroxy ester even though the salt was carefully hydrolyzed at −10°.

(13) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

(14) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963, p 315.

(15) Melting points, taken on a Thomas–Hoover capillary melting point apparatus, are corrected. Boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., or on an F & M Model 185 C,H,N-Analyzer. All infrared spectra were obtained in *ca.* 10% carbon tetrachloride solution in a 0.05-mm sodium chloride cell on a Beckman IR-8 double-beam recording spectrometer with a 6101-cm^{-1} peak from polystyrene *vs.* air as a calibration point. Nuclear magnetic resonance spectra were obtained on a Varian A-60 or A-60A as a solution in carbon tetrachloride containing tetramethylsilane. Chemical shifts are designated by the τ scale.

(16) C. E. Maxwell, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 305.

(17) S. G. Beech, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 4686 (1952).

(18) The use of temperatures in excess of 25° or the presence of acetic anhydride in the lead tetraacetate greatly reduced the yield of **4**.

(19) E. D. Knott, *J. Chem. Soc.*, 1190 (1947).

Physical constants and analytical data for the cyclopropyl acetates are presented in Table V. Spectral data are summarized in Table VI.

TABLE V

PHYSICAL CONSTANTS AND ANALYSES OF 1-ARYLCYCLOPROPYL ACETATES

		Calcd, %			Found, %		
Substituent	Mp, °C	C	H	N	C	H	N
H (5a)	Oil[a]	...	...	...	...	...	...
p-CH_3 (5b)	34–35.5	75.76	7.42	...	75.98	7.48	...
p-CH_3O (5c)	36.8–37.7	69.88	6.84	...	70.23	7.06	...
m-CH_3O (5d)	Oil[b]	69.88	6.84	...	70.88	7.00	...
m-NO_2 (5e)	84.3–86.3	59.72	5.01	6.33	59.66	5.05	6.38
p-Br (5f)	57.5–59.5	51.79	4.35	...	52.09	4.51	...
p-Cl (5g)	67.0–69.4	62.72	5.26	...	63.03	5.30	...
m-Br (5h)	Oil[c]	51.79	4.35	...	51.59	4.34	...

[a] Bp 63–70° (0.40–0.45 mm); lit.[5] bp 68–70° (0.4 mm). [b] Bp 98° (0.40 mm) and 109° (0.75 mm). [c] Bp 100° (0.68 mm).

TABLE VI

SPECTRAL DATA ON 1-ARYLCYCLOPROPYL ACETATES[a]

Substituent	
H (5a)	Nmr: 2.57–2.90, m, 5 H; 8.12, s, 1 H; 8.75–8.92, m, 4 H
	Infrared: 3033, 1748, 1369, 1243, 1204, 1026, 990
p-CH_3 (5b)	Nmr: 2.67–3.11, m, 4 H; 7.73, s, 3 H; 8.12, s, 3 H; 8.80–9.00, m, 4 H
	Infrared: 3029, 1747, 1370, 1349, 1240–1180, 1100, 988
p-CH_3O (5c)	Nmr: 2.52–3.38, m, 4 H; 6.26, s, 3 H; 8.11, s, 3 H; 8.83–9.03, m, 4 H
	Infrared: 3010, 2950, 2840, 1750, 1613, 1517, 1368, 1349, 1300, 1246, 1204, 1175, 1030, 986
m-CH_3O (5d)	Nmr: 2.71–3.44, m, 4 H; 6.33, s, 3 H; 8.12, s, 3 H; 8.79–8.95, m, 4 H
	Infrared: 3006, 2941, 2837, 1755, 1605, 1587, 1457, 1370, 1234, 1205, 1047, 1026
m-NO_2 (5e)	Nmr: 1.77–2.68, m, 4 H; 8.00, s, 3 H, 8.60–8.80, m, 4 H
	Infrared: 3090, 1759, 1532, 1354, 1369, 1242, 1207
p-(Br (5f)	Nmr: 2.50–2.92, m, 4 H; 8.08, s, 3 H, 8.72–8.90, m, 4 H
	Infrared: 3015, 1751, 1495, 1368, 1240, 1204, 1097, 1026, 1010
p-Cl (5g)	Nmr: 2.75, s, 4 H; 8.06, s, 3 H, 8.75–8.95, m, 4 H
	Infrared: 3017, 1753, 1499, 1370, 1241, 1203, 1100, 1026, 1015, 997
m-Br (5h)	Nmr: 2.41–2.97, m, 4 H; 8.10, s, 3 H; 8.68–8.90, m, 4 H
	Infrared: 3024, 1741, 1566, 1480, 1451, 1411, 1366, 1338, 1240–1190, 1070, 1024, 990

[a] Nmr data indicate the chemical shift (τ scale), multiplicity, and integrated area. Infrared absorptions are expressed in cm^{-1}.

1-(*p*-Anisyl)cyclopropanol was prepared from 1-*p*-anisylcyclopropyl acetates by treatment of the acetate in ether with excess lithium aluminum hydride followed by an aqueous work-up. The nmr spectrum of the alcohol, mp 62–63°, showed a complex multiplet at 3.07 (4 H), a singlet at 6.28 (3 H), a broad singlet at 6.68 (1 H), and a complex multiplet at 9.06 (4 H), Infrared peaks occurred at 3600, 3500–3150, 3002, 2952, 2833, 1614, 1516, 1247, 1220, 1178, 1038, 1011, and 827–734 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; O, 19.48. Found: C, 72.92; H, 7.41; O, 19.68.

1-(*p*-Chlorophenyl)cyclopropanol, mp 68–69°, was prepared from the acetate in the manner described above. The nmr spectrum showed a complex multiplet at 2.83 (4 H), a broad singlet at 6.30 (1 H), and a complex multiplet at 9.00 (4 H). Significant peaks in the infrared spectrum occurred at 3600,

(20) L. N. Nobles and J. H. Burckhalter, *J. Amer. Pharm. Soc., Sci. Educ.*, **47**, 77 (1958).

3530–3130, 3091, 3010, 1498, 1222, 1100, 1013, 866, and 820–734 cm^{-1}.

Anal. Calcd for C_6H_9ClO: C, 64.11; H, 5.38. Found: C, 63.94; H, 5.33.

1-*p*-Anisyl-1-acetoxypropene was prepared by passing ketene through molten *p*-methoxypropiophenone (100 g, 0.61 mol, Aldrich) for 15.5 hr with 10 drops of concentrated H_2SO_4 as catalyst. Two washings with aqueous base and several with water followed by an ether work-up gave a viscous brown liquid which was distilled on a 14-in. wire, spiral column to give a high-boiling fraction, bp 115–150° (0.4 mm), which was recrystallized twice from *n*-pentane and twice from ethanol. The product, mp 49–50°, gave an nmr spectrum which showed a complex multiplet at 2.98 (4 H), a quartet at 4.36 (1 H, J = 7 cps), a singlet at 6.28 (3 H), a singlet at 7.73 (3 H), and a doublet at 8.36 (3 N, J = 7 cps). Significant peaks in the infrared spectrum were found at 3000, 2936, 2838, 1760, 1611, 1509, 1465, 1441, 1368, 1313 (sh), 1307, 1282, 1247, 1206, 1175, 1111, 1040 (sh), 1027, 834, and 814 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84; O, 23.27. Found: C, 69.61; H, 6.78; O, 23.50.

Acid hydrolysis (0.1 N HCl) at 55° in 50 wt % aqueous dioxane resulted in a pseudo-first-order constant of 1.086×10^{-4} sec^{-1}.

1-*p*-Anisyl-1-acetoxypropane.—1-*p*-Anisyl-1-propanol (21 g, 0.126 mol), prepared by the addition of *p*-methoxyphenylmagnesium bromide to propionaldehyde, and dimethylaniline (45.9 g, 0.378 mol, Eastman) in ether (150 ml) were stirred at 5° while acetyl chloride (29.7 g, 0.378 mol) was added dropwise. The solution was maintained at reflux for 62 hr and worked up in the usual manner with ether and water to give the desired product, bp 94–96° (0.31 mm). The nmr spectrum showed a complex multiplet at 2.74–3.31 (4 H), a triplet at 4.43 (1 H, J = 7 cps), a singlet at 6.32 (3 H), a singlet at 8.07 (3 H), a multiplet at 8.05–8.43 (2 H), and a triplet at 9.17 (3 H, J = 7 cps).

Acid hydrolysis (0.1 N HCl) at 40° in 50 wt % aqueous dioxane resulted in a pseudo-first-order constant of 1.025×10^{-3} sec^{-1}.

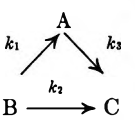
Kinetic Procedure. At 40°.—Approximately 0.001 or 0.002 mol of ester weighed to the nearest 0.0001 g was placed into a clean, dry 25-ml volumetric flask to which an acid solution (25 ml), *vide infra*, was introduced with a volumetric pipet, and the total volume was estimated to the nearest 0.01 ml *via* calibration marks on the neck of the volumetric flask. Corrected acid and ester concentrations were calculated at 40°, and the stoppered flask was immersed in a constant temperature bath. Aliquots (*ca.* 1 ml) of known volume to 0.0001 ml were withdrawn at intervals of 1 hr, diluted with 25.00 ml of distilled water and titrated with a standardized solution of sodium methoxide in methanol to a phenophthalein end point.

At 55 and 70°.—When the ester and acid had been combined, *ca.* 1.4-ml portions were sealed in 100-mm test tubes packed in ice and the sealed tubes were then immersed in a constant temperature bath. At the appropriate time interval a tube was removed from the bath, cooled for several minutes in water, and broken. An accurate aliquot was treated as previously indicated. Intervals of 7.5–30 min were used.

The acid solution was prepared by the addition of the appropriate volume of dry hydrogen chloride to equal weights of *p*-dioxane (purified by passage through Woelm, acid-washed alumina (I) and distillation from sodium) and water so as to give an *ca.* 0.1 M acid solution. Standardization was accomplished with a solution of sodium methoxide (Matheson Coleman and Bell) in anhydrous methanol. The latter was standardized with potassium hydrogen phthalate.

All titrations were performed with a 5-ml self-filling buret (readable to 0.001 ml) with a stoppered reservoir. Three drops of a solution of 1 g of phenolphthalein in 50 ml of ethanol and 50 ml of water were used. The polyurethane insulated constant temperature bath was maintained at ±0.01° with a solid-state electronic thermostating circuit.

Calculations.—The derivation of eq 1 is given below. If we let cyclopropyl ester = B, intermediate ester = A, and acetic acid = C, the differential equations which describe the indicated kinetic system are as follows.



$$\frac{dB}{dt} = -(k_1 + k_2)B \quad (2)$$

$$\frac{dA}{dt} = k_1B - k_3A \quad (3)$$

$$\frac{dC}{dt} = k_2B + k_3A \quad (4)$$

Integration of eq 2 and introduction of the initial conditions that $B = B_0$ at $t = 0$ gives

$$B = B_0e^{-(k_1+k_2)t}$$

Substitution of this value for B into eq 3, application of the integrating factor e^{k_3t}, and introduction of the condition that $A = 0$ at $t = 0$ leads to the following solution to the linear differential equation.

$$A = [B_0k_1/(k_3 - k_1 - k_2)]\,[e^{-(k_1+k_2)t} - e^{-k_3t}]$$

Substitution of the values for A and B into eq 4, separation of variables, integration, and introduction of the condition that $C = 0$ at $t = 0$ gives

$$C = B_0 + [B_0/(k_1 + k_2 - k_3)]\,[(k_3 - k_2)\,e^{-(k_1+k_2)t} - k_1e^{-k_3t}]$$

The fraction of reaction, $X = C/B_0$ is then equal to eq 1.

Typical pseudo-first-order rate data are given in Table VII for the hydrolysis of 1-(*m*-bromophenyl)cyclopropyl acetate in 50 wt % aqueous dioxane at 40.00 ± 0.02° in the presence of 0.1119 M hydrochloric acid. The initial ester concentration was 0.05302 M. All pseudo-first-order runs were followed to *ca.* 25% reaction except for 1-(*m*-nitrophenyl)cyclopropyl acetate which was only followed to *ca.* 15% reaction.

TABLE VII

Time, sec	Titer, ml[a]	Ln [a/(a − x)]	Time, sec	Titer, ml[a]	Ln [a/(a − x)]
3,600	3.220	0.0200	25,200	3.365	0.1231
7,440	3.240	0.0336	28,931	3.380	0.1343
11,140	3.268	0.0530	32,500	3.404	0.1527
14,400	3.292	0.0699	39,600	3.442	0.1824
18,000	3.314	0.0856	43,290	3.461	0.1976
21,680	3.332	0.0987	46,860	3.488	0.2196
			64,800	3.580	0.2985

[a] 0.03399 N sodium methoxide in methanol; $k = 4.016 \times 10^{-5}$ sec^{-1}.

Typical non-first-order data are given in Table VIII for the hydrolysis of 1-(*p*-tolyl)cyclopropyl acetate in 50 wt % aqueous dioxane at 40.00 ± 0.02° in the presence of 0.12026 M hydrochloric acid. The initial ester concentration was 0.06646 M.

TABLE VIII

Time, sec	Titer, ml[a]	% hydrolyzed	Time, sec	Titer, ml[a]	% hydrolyzed
3,624	3.437	0.79	32,370	4.062	33.89
7,326	3.530	5.71	39,630	4.122	37.01
10,940	3.700	14.70	43,200	4.140	39.67
14,420	3.844	22.31	46,950	4.178	39.97
18,096	3.920	26.33	50,400	4.203	41.29
21,560	3.958	28.34	54,110	4.244	43.46
25,215	3.995	30.30	57,600	4.266	44.63
28,770	4.030	32.15			

[a] 0.03405 N sodium methoxide in methanol.

Registry No.—**5a**, 16031-49-5; **5b**, 16031-50-8; **5c**, 16031-51-9; **5d**, 16109-33-4; **5e**, 15973-63-4; **5f**, 16031-52-0; **5g**, 16031-53-1; **5h**, 15973-64-5; 1-(*p*-anisyl)cyclopropanol, 15973-65-6; 1-(*p*-chlorophenyl)cyclopropanol, 16031-54-2; 1-*p*-anisyl-1-acetoxypropene, 16031-56-4; 1-*p*-anisyl-1-acetoxypropane, 16031-55-3.

Nitrile Oxides. XI. Dimerization of a Sterically Hindered Nitrile Oxide. Dimesitylfurazan Oxide[1]

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Received August 7, 1967

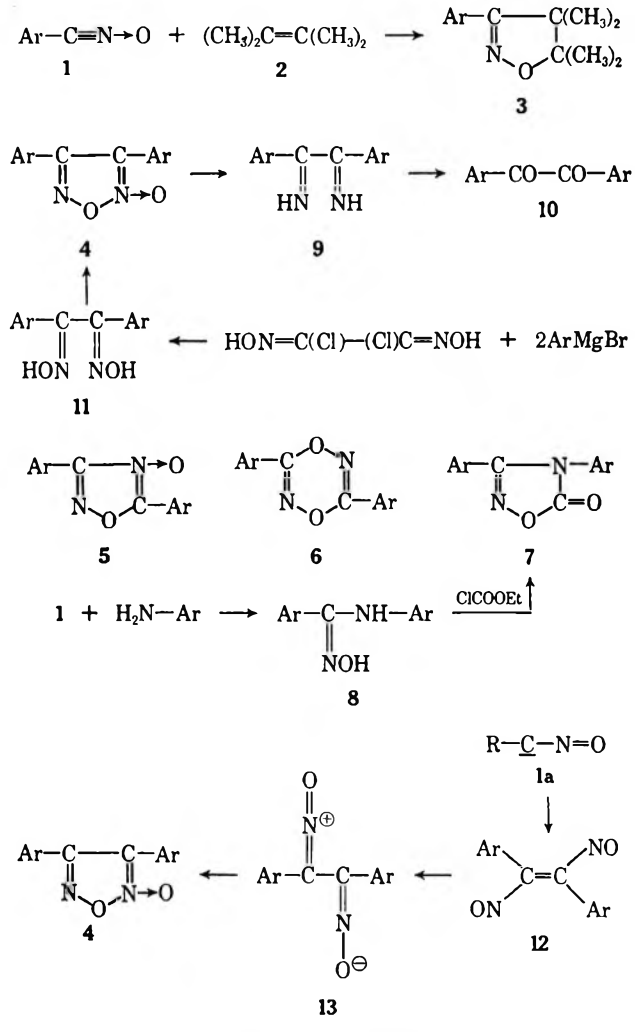
Contrary to earlier reports, mesitonitrile oxide (**1**), under very specific conditions, may form a dimer for which the structure of dimesitylfurazan oxide (**4**) was ascertained by mass spectrum, chemical degradation, and an independent synthesis. Sterical considerations require the dimerization of **1** to **4** to proceed *via* a nitrosocarbene intermediate.

It was reported in earlier communications that aromatic nitrile oxides sterically hindered by substituents of appropriate size in *ortho,ortho* position will not undergo the spontaneous dimerization to furazan oxides (furoxans, 1,2,5-oxadiazole 1-oxides), generally characteristic of nitrile oxides.[1,2] At temperatures above 100°, these nitrile oxides rearranged neatly to the corresponding isocyanates.

The remarkable stability of mesitonitrile oxide (**1**), for instance, was demonstrated by the successful 1,3-dipolar cycloaddition to 2,3-dimethylbutene-2 (**2**), an extremely unreactive olefin. Heretofore, tetrasubstituted ethylenes were generally considered inert toward nitrile oxides.[3] During the reaction of **1** with **2** which required refluxing for 21 hr in an excess of the hydrocarbon, besides a 18% yield of 4,4,5,5-tetramethyl-3-mesityl-4,5-dihydroisoxazole (**3**) and a major amount of mesityl isocyanate, 12% of a dimer of **1**, melting at 130°, was obtained. The same dimer was formed in approximately the same yield when **1** was refluxed for 24–48 hr with a petroleum fraction, free of olefins, boiling at ~65°. The main product under these conditions was mesityl isocyanate. The formation of the dimer is restricted to a rather narrow temperature range; at 50° **1** remained mostly unchanged over comparable reaction times, while at temperatures above 75°, the rearrangement to the isocyanate predominates. If **1** was heated quickly to reflux in an inert higher boiling solvent, such as ligroin (bp 100–110°) or toluene, an almost quantitative conversion to mesityl isocyanate was observed.[2b]

For reasons of analogy, it seemed obvious to assume that the dimer had the structure of a dimesitylfurazan oxide (**4**), were it not for extreme steric hindrance involved in the direct head to head combination of two molecules of **1** to **4**. Further doubt on the furazan oxide structure was cast by the impossibility of deoxygenating the dimer to the corresponding furazan (1,2,5-oxadiazole) by means of trivalent phosphorus compounds, a reaction generally applicable to all furazan oxides investigated so far.[4]

Therefore, the less sterically hindered structures **5**, **6**, or **7** had to be considered too. Structures **5** and **6** would both result from a head to tail dimerization of **1**, while **7** would require 1,3-dipolar cycloaddition of **1** to mesityl isocyanate, shown to be present in the reaction mixture. Formula **7** was ruled out by an independent synthesis. Mesitonitrile oxide (**1**) added mesidine to form mesito-



N-mesitylamidoxime (**8**).[5] Compound **8** reacted with ethyl chloroformate under ring closure directly to **7**. The synthetic product was different from the dimer. The infrared spectrum of the dimer is complex (as is that of known diarylfurazan oxides[6]), all major bands are compatible with structure **4**. Since nothing is known about the spectral differences between the furazan oxides and the ring systems **5** and **6**, no valid conclusions can be drawn.

The mass spectrum shows, in addition to the parent peak (322), major peaks at 306, 262, 161, and 145. The first one, corresponding to loss of one oxygen, is indica-

(1) Previous communication: C. Grundmann and R. Richter, *J. Org. Chem.*, **33**, 476 (1968).

(2) (a) C. Grundmann and J. M. Dean, *Angew. Chem.*, **76**, 682 (1964); (b) C. Grundmann and J. M. Dean, *J. Org. Chem.*, **30**, 2809 (1965); (c) C. Grundmann, *Fortschr. Chem. Forsch.*, **7**, 62 (1966).

(3) R. Huisgen, *Angew. Chem.*, **75**, 604 (1963).

(4) C. Grundmann, *Chem. Ber.*, **97**, 575 (1964).

(5) C. Grundmann and H.-D. Frommeld, *J. Org. Chem.*, **31**, 157 (1965).

(6) (a) N. E. Boyer, G. M. Czerniak, H. S. Gutkowsky, and H. R. Synder, *J. Amer. Chem. Soc.*, **77**, 4238 (1955); (b) J. H. Boyer, U. Toggweiler, and G. A. Stoner, *ibid.*, **79**, 1748 (1957).

tive of a heterocyclic N-oxide,[7] thus ruling out structure **6**. The peak at 262 corresponds to loss of the fragment N_2O_2 (60) which is only compatible with the furoxan structure **4** for the dimer, while the peaks at 161 and 145 corresponding to mesitonitrile oxide and mesitonitrile are of no diagnostic value. Under the same conditions, diphenylfurazan oxide shows a strictly analogous pattern with strong peaks at P-16 and P-60.

Reduction of the dimer with zinc and acetic acid did not produce the mesitildioxime (**11**), as expected from analogous experience with other diarylfurazan oxides,[8] but a base $C_{20}H_{24}N_2$, which turned out to be mesitildiimine (**9**). Contrary to the other known ketimines, the compound is surprisingly stable to hydrolysis, but treatment with boiling 2 *N* sulfuric acid converted it neatly into mesityl diketone (**10**) (mesitil), identical with a specimen prepared according to the literature.[9]

Finally, the structure of the dimer was proved by an independent synthesis. Mesitylmagnesium bromide reacted with dichloroglyoxime to mesitildioxime (**11**), a compound which cannot be obtained by oximation of **10**.[10] Dehydrogenation of **11** with sodium hypobromite gave dimesitylfurazan oxide (**4**) identical with the dimer of I.

Although furazan oxide formation from nitrile oxides is probably the longest known reaction of this class of compounds, it is still the least understood mechanistically. 1,3-Dipolar cycloaddition is ruled out, since it violates the principle of maximum gain in σ bonding invariably found valid in all of the many other types of such cycloadditions. Furthermore, 1,3-dipolar cycloaddition, being firmly established as a concerted (four-center, "no mechanism") addition[11] is virtually impossible for steric reasons in the case of mesitonitrile oxide. We are, therefore, inclined to assume that the formation of the furazan oxide might occur—at least in this case—in a multistep reaction by the dimerization of the nitrile oxide to 1,2-dinitrosoethylene **12**, involving the mesomeric structure **1a** with carbene character as first suggested by Huisgen. The transient intermediate **12** rearranges then *via* the dipolar structure **13** to the furazan oxide **4**.

Studies of Stuart–Briegleb models which are supposed to represent a close approximation to the actual spatial requirements or organic molecules indicate that even in the case of the sterically hindered mesitonitrile oxide such a route would still be possible,[12] although the intermediate **12** could only exist in the *trans* configuration. Nevertheless, **4** is a very rigid structure with both aromatic rings twisted severely out of plane with the furazan ring. Even in diphenylfurazan oxide both aromatic rings, although they may rotate freely, cannot be brought simultaneously in one plane with the heterocyclic ring. One would, therefore, expect little difference in the ultraviolet spectra of both compounds; the observed data, however, are in the right direction, showing a hypsochromic shift of the first band of **4** as compared with diphenylfurazan oxide.

In conclusion, the formation of dimesitylfurazan oxide from mesitonitrile oxide might be the first experimental evidence for Huisgen's mechanism, since no other pathway suggested so far for this dimerization could overcome the steric restrictions of this case.

Experimental Section[13]

Reaction of Mesitonitrile Oxide with 2,3-Dimethylbutene-2.—Mesitonitrile oxide (2.0 g) and 2,3-dimethylbutene-2 (4 ml) were heated for 12 hr to 64°, then refluxed (71°) for an additional 9 hr. The reaction mixture, diluted with 200 ml of cyclohexane, was chromatographed through a column of basic aluminum oxide (Woelm). The filtrate and the cyclohexane washings contained only mesityl isocyanate identified as reported earlier.[2b] Benzene extracted from the column a fraction (345 mg) which yielded after recrystallization from methanol 240 mg (12%) of dimesitylfurazan oxide (**4**), mp 129–130°. Further extraction with benzene–ether (50:1) gave a fraction (550 mg, 18%) of 4,4,5,5-tetramethyl-3-mesityl-4,5-dihydroisoxazole (**3**), mp 71°, after recrystallization from petroleum ether (bp 35–45°).

Anal. Calcd for $C_{16}H_{22}NO$: C, 78.32; H, 9.45; N, 5.71; mol wt, 245. Found: C, 78.17; H, 9.50; N, 5.64; mol wt, 240 (osmometric, acetone).

Dimesitylfurazan Oxide from Mesitonitrile Oxide.—Mesitonitrile oxide (1.61 g) and 30 ml of ligroin,[14] bp 60–65° (the minimum amount to afford a homogeneous reaction mixture at the boiling point), were refluxed for 48 hr with exclusion of moisture. The reaction mixture was filtered from small amounts of insolubles, if necessary, then the solvent removed by distillation and the residue subjected to vacuum sublimation in a cold finger apparatus, cooled with Dry Ice and acetone. At 0.01 mm and 40–65° bath temperature, all mesityl isocyanate collected at the condenser within 2–3 hr. The residue was dissolved in methanol (5 ml) and kept overnight at −10°, whereby 320 mg (20%) of dimesitylfurazan oxide (**4**) separated. After two recrystallization from methanol colorless shiny leaflets were obtained, mp 133°.

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69; mol wt, 322. Found: C, 74.67; H, 7.05; N, 8.61; mol wt, 314, 321 (osmometric, acetone or chloroform).

The ultraviolet spectrum of **4** (in ethanol) showed bands at λ_{max} 273 mμ (° 11,000) and diphenyfuroxan (inethanol) showed bands at λ_{max} 283 mμ (ε 5700).[6b]

The mass spectra of **4** and diphenylfurazan oxide were determined with the Associated Electrical Industries double focusing mass spectrograph MS 9, 8000 V, 70 eV, temp <250°.

Mesito-N-mesitylamidoxime (8).—Mesitonitrile oxide (0.5 g) and mesidine (0.5 g) were refluxed in methanol (20 ml) for 5 min. Upon gradual dilution with H_2O, the amidoxime crystallized. One recrystallization from methanol yielded 550 mg of pure **8**, mp 202–203° dec.

Anal. Calcd for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45. Found: C, 77.25; H, 8.30; N, 9.22.

3,4-Dimesityl-4,5-dihydro-1,2,4-oxadiazolone-5 (7).—Compound **8** (190 mg) and ethyl chloroformate (0.7 ml) were refluxed for 3 hr in chloroform (20 ml). After evaporation of the solvent the residue crystallized on addition of methanol and scratching, 140 mg of **7**, mp 155–156°, were obtained after one recrystallization from methanol.

Anal. Calcd for $C_{20}H_{22}N_2O_2$: N, 8.69. Found: N, 8.75.

Mesitildiimine (9).—Dimesitylfurazan oxide (771 mg) was dissolved on the steam bath in acetic acid (40 ml) and H_2O (8 ml), 8 g of zinc granules (50 mesh) added, the reaction mixture stirred for 4.5 hr at 80–90°, filtered hot, and the undissolved metal washed with 12 ml of acetic acid water (5:1). After addition of 50 ml of H_2O, 24 mg of neutral by-products separated overnight at 0° and were removed by filtration. The filtrate

(7) A. Chatterjee, P. L. Majunder, and A. B. Ray, *Tetrahedron Lett.*, 159 (1965); T. A. Bryce and J. R. Maxwell, *Chem. Commun.*, 206 (1965).

(8) J. V. R. Kaufman and J. P. Picard, *Chem. Rev.*, **59**, 429 (1959).

(9) R. C. Fuson and T. Corse, *J. Amer. Chem. Soc.*, **60**, 2066 (1938).

(10) E. P. Kohler and R. Baltzly, *ibid.*, **54**, 4015 (1932).

(11) R. Huisgen, *Angew. Chem.*, **75**, 742 (1963).

(12) It must be noted, however, that completely valid conclusions cannot be drawn from these studies, since the appropriate building blocks for some of the structures under consideration do not yet exist, *e.g.*, for —C≡N→O or =N→O in a five-membered ring. But the above considerations are still valid for mesitonitrile which can be built and is certainly less crowded as **1** as far as the C atom involved is concerned. Dimesityl-1,2,5-oxadiazole can be constructed, and it is easily seen on the model that the additional oxygen at N^2 present in **4**, adds little if anything to the steric requirements.

(13) Melting points were determined with the Fisher–Johns melting point apparatus and are uncorrected. Microanalyses were by Galbraith Laboratories, Knoxville, Tenn.

(14) Commercially available Skellysolve B was redistilled and the fraction boiling within the above given limits was used.

was evaporated at the water pump to dryness from a 60° water bath and the residue distilled again to dryness twice after adding each time 25 ml of H_2O in order to complete the removal of acetic acid. The residue dissolved mostly at room temperature in 50 ml of 2 *N* hydrochloric acid. Again, insoluble neutral products were filtered, and the filtrate was oversaturated with concentrated ammonia, whereupon a crystalline precipitate of **9** (542 mg, 76%) was obtained. After repeated recrystallizations from ligroin slightly yellowish compact prisms, mp 182–183°, were obtained.

Anal. Calcd for $C_{20}H_{24}N_2$: C, 82.14; H, 8.27; N, 9.58; mol wt, 292. Found: C, 81.95; H, 8.25; N, 9.38; mol wt, 291 (osmometric, acetone).

Mesitildiimine was also obtained in 66% yield from mesitildioxime (**11**) by the same procedure. The reduction of dimesitylfurazan oxide with sodium and ethanol gave **9** in 59% yield. Compound **4** was not affected by tin(II) chloride in boiling methanol or by heating with an excess of tri-*n*-butylphosphine for 3 hr to 140°.

Heating **9** (148 mg) with acetic anhydride (4 ml) for 4 hr to 100° yielded on cooling N,N′-diacetylmesitilidiimine (148 mg, 78%). After recrystallization from methanol, pale yellow needles, mp 264°, were obtained.

Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44; mol wt, 376. Found: C, 76.27; H, 7.67; N, 7.26; mol wt, 379 (osmometric, chloroform).

N,N′-Dibenzoylmesitildiimine was obtained in 36% yield by benzoylation of **9** with benzoyl chloride and pyridine in the usual manner. After crystallization from ether, it melted at 247°.

Anal. Calcd for $C_{34}H_{32}N_2O_2$: C, 81.57; H, 6.44. Found: C, 81.74; H, 6.59.

Hydrolysis of Mesitildiimine.—Mesitildiimine (0.3 g) was heated on the steam bath for 3 hr with 30 ml of 2 *N* sulfuric acid whereby a yellow solid precipitated gradually from the solution. After cooling, the formed product was filtered and washed with water (0.25 g, 85%). One recrystallization yielded pure mesitil (**10**), mp 122°, identical with an authentic specimen.[9] Compound **10** was further characterized by oxidation with sodium peroxide to mesitoic acid according to the procedure given in the literature.[10]

Mesitildioxime (11).—A solution of mesitylmagnesium bromide was prepared from bromomesitylene (80 g), ethylene bromide (40 g), and magnesium turnings (17.5 g) in tetrahydrofuran (100 ml). To avoid precipitation of the Grignard compound 150 ml of tetrahydrofuran was added on completion of the reaction. With ice cooling, a solution of dichloroglyoxime (16 g) in tetrahydrofuran (150 ml) was then added dropwise within 2 hr. After the reaction mixture was left overnight at 25°, 300 ml of the solvent were removed by distillation and the residue was decomposed with ice and saturated ammonium chloride solution. The precipitated **11** was filtered off and was washed thoroughly with dilute hydrochloric acid and H_2O. The dioxime has a strong tendency to adsorb inorganic salts. The crude **11** (22 g, 70%) was recrystallized from dioxane or, preferably, acetic acid, mp 310° dec. A dioxime of structure **11** can occur in several stereoisomers; it has not been ascertained whether this material was uniform in this respect.

Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 73.96; H, 7.60; N, 8.42.

Dimesitylfurazan Oxide from Mesitildioxime.—Mesitildioxime (3.2 g) was dissolved in warm pyridine (100 ml) and 1 *N* sodium hydroxide (100 ml). Water (50 ml) was added, and the solution, which must remain clear, cooled quickly to 5°. Within 30 min, a cold solution of 1.6 g of bromine in 100 ml of 2 *N* sodium hydroxide was added with stirring. After 2 hr, the precipitate was filtered and washed with water. The dimesitylfurazan oxide (**4**) thus obtained (2.4 g, 75%, mp 130°) was almost pure. One recrystallization from ethanol yielded a product, mp 132°, which did not depress the melting point of a specimen prepared from mesitonitrile oxide. The infrared spectra of both samples were strictly superimposable.

Registry No.—**3**, 16031-57-5; **4**, 16031-58-6; **7**, 16031-59-7; **8**, 16031-60-0; **9**, 16031-61-1; **10**, 4746-81-0; **11**, 16031-62-2; N,N′-diacetylmesityldiimine 16031-64-4; N,N′-dibenzoylmesityldiimine, 16031-63-3.

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A Study of the Interaction of 1,3-Diaxial Sulfur Atoms

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A series of ethylene thioketals was prepared by the reaction of 1,3-cyclohexanediones and phloroglucinol with ethanedithiol. The uv spectra and physical properties of these compounds are discussed.

In the reaction between 5,5-dimethyl-1,3-cyclohexanedione and ethanedithiol the bisthioketal, 13,13-dimethyl-1,4,8,11-tetrathiadispiro[4.1.4.3]tetradecane, was isolated. It was noted that compound **4** possessed ultraviolet absorption at 246 mμ which was similar to values reported for acyclic mercaptols. The absorption for cyclic thioketals can be ascribed to resonance interactions as proposed by Fehnel and Carmack.[2]

The distance between the 1,3-diaxial sulfur atoms in **4** is relatively close to that between sulfur atoms in the thioketal ring. This suggested the possibility of the occurrence of 1,3-diaxial sulfur interactions as well as the interactions present within the thioketal ring.

A series of mono-, di-, and triethylene thioketals was synthesized and the ultraviolet spectra studied to determine if 1,3-diaxial and 1,3,5-triaxial sulfur orbital interactions do exist. The observed maxima and extinction coefficients are given in Table I.

The results indicate that there is no marked interaction between 1,3-diaxial sulfur atoms since the long wavelength absorption at 246 mμ remains constant for the series of thioketals studied. The additive effect in the molar extinction coefficients are approximately the values which would be expected with multiple chromophores. However, a proportionately larger increase in the molar extinction coefficient was observed on the introduction of a second thioketal grouping β to the first in the parent compound 1,4-dithiaspiro[4.5]decane (**1**). A simple additive effect would give an extinction coefficient of ~630 but the observed values were 748, 729, and 728, respectively, for **2**,

(1) Taken in part from the dissertation presented by J. L. Diebold, 1964, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Ph.D. Degree.

(2) E. A. Fehnel and M. Carmack, *J. Amer. Chem. Soc.*, **71**, 84 (1959).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA[a]

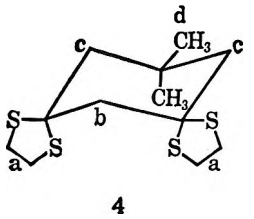
Compd	1,2-Dichloroethane[b] λ, mμ	1,2-Dichloroethane[b] ε[d]	Acetonitrile[c] λ, mμ	Acetonitrile[c] ε[d]
1[e,f]	246	315	242	295
2	246	758	243	628
3	246	729	243	622
4	246	723	244	621
5	246	1030		
6[f]	246	662	243	560

[a] Recorded on a Bausch and Lomb Spectronic 505. [b] Reagent grade. [c] Spectrograde. [d] Molar extinction coefficient. [e] We are indebted to M. P. Mertes for a sample. [f] λ_{max}^{MeOH} 243 mμ (ε 283).

3, and 4, thus indicating a deviation of approximately 15% from the theoretical value.

When a third thioketal, compound 5, was introduced β to the other two, it appears that the chromophoric increment is about the predicted value obtained by adding the values for the dithioketal and the monothioketal. Support for the presence of a definite effect upon the introduction of a second thioketal β to the first is given by the values recorded for the 1,4 isomer, 6. The value for the extinction coefficient in 1,2-dichloroethane is 662 which is a deviation of only 32 from the calculated value as compared to 128 in the 1,3 isomer, 2.

The assumption that the axial sulfur atoms can interact requires the cyclohexane ring to remain in a true chair or certain boat conformations. The very close approach of the 1,3-diaxial sulfur atoms and their large bulk could cause distortion of the cyclohexane ring. This possibility is increased by the introduction of methyl 1,3-nonbonded interactions as would occur in 4. The appearance of only one signal



4

for the *gem*-dimethyl group in the nmr spectrum of 4 could indicate such distortion results in the equalization of the environments of the methyl groups. The most likely conformation would then be a twist or skew-boat in which the sulfur atoms are at a maximum distance from each other. The nmr signal is not sufficient proof of the presence of a twist form, since the possibility exists that the thioketal sulfur atoms could modify the magnetic susceptibility of one of the methyl groups enough to cause both methyl peaks to be superimposable or the signal could be due to rapid ring inversion.

The 1,3,5-trisubstituted system (5) would be expected to have the possibility of resonance stabilization in the 1,3,5-triaxial form owing to an overlap of the sulfur orbitals. However, the steric crowding of the sulfur atoms may cause ring distortion which would prevent orbital overlap. It is apparent that no major interaction of sulfurs other than that within the thioketal occurs in this system.

It was possible to oxidize 4 to the corresponding tetrasulfone in the presence of trifluoroperoxy acetic acid. A similar attempt to oxidize 5 to the corresponding hexasulfone failed to go to completion, but produced a mixture having nine to eleven oxygens present per molecule.

Experimental Section[3]

1,4,8,11-Tetrathiadispiro[4.1.4.3]tetradecane (2).—Boron trifluoride etherate (6.33 g, 0.0446 mol) was added during 1.5 hr to a stirred solution of 2.5 g (0.0223 mol) of dihydroresorcinol and 4.2 g (0.0446 mol) of ethanedithiol in 60 ml of tetrahydrofuran at room temperature. After 2 days the solution was diluted with 250 ml of hot water and the white crystalline precipitate was collected. Recrystallization from isopropyl ether gave 1,4,8,-11-tetrathiadispiro[4.1.4.3]tetradecane in a 80% yield: mp 158–158.5°; for uv data see Table I; nmr, δ 3.28 (H_a see structure 4), 2.73 H_b, 1.93 H_c.

Anal. Calcd for $C_{10}H_{16}S_4$: C, 45.41; H, 6.10; S, 48.49. Found: C, 45.45; H, 6.12; S, 48.28.

1,4,8,11-Tetrathiadispiro[4.1.4.3]tetradecan-13-ol (3).—Boron trifluoride etherate (3.78 g, 0.0265 mol) was added during 15 min to a stirred solution of 1.70 g (0.0133 mol) of dihydrophloroglucinol and 2.5 g (0.0265 mol) of ethanedithiol in 20 ml of glacial acetic acid at room temperature. After 1 day the product was collected. The residue from the evaporated mother liquor and the product were both washed with hot water to remove any starting material. Recrystallization from 1,2-dichloroethane gave 2 g of white crystalline 1,4,8,11-tetrathiodispiro[4.1.4.3]-tetradecan-13-ol in a 54% yield: mp 208–209°; for uv data see Table I; nmr, δ 3.31 H_a, 2.66 H_b.

Anal. Calcd for $C_{10}H_{16}S_4O$: C, 42.82; H, 5.75; S, 45.73. Found: C, 43.04; H, 5.89; S, 45.70.

13,13-Dimethyl-1,4,8,11-tetrathiadispiro[4.1.4.3]tetradecane (4).—Boron trifluoride etherate (5.63 g, 0.0396 mol) was added during 30 min to a stirred solution of 4.15 g (0.044[illegible] mol) of ethanedithiol and 5 g (0.0357 mol) of 5,5-dimethyl-1,3-cyclohexanedione in 75 ml of glacial acetic acid and heated to 70°. After 1 day the product was collected. Concentration of the filtrate gave a total yield of 3 g (29%) of 13,13-dimethyl-1,4,8,11-tetrathiadispiro[4.1.4.3]tetradecane. Recrystallization from glacial acetic acid gave white needles: mp 176.5–177°; for uv data see Table I; nmr, δ 3.28 H_a, 2.68 H_b, 1.98 H_c, 1.15 H_d.

Anal. Calcd for $C_{12}H_{20}S_4$: C, 49.27; H, 6.89; S, 43.84. Found: C, 49.33; H, 6.75; S, 43.66.

1,4,8,11,14,17-Hexthiatrispiro[4.1.4.1.4.1]octadecane (5).—Phloroglucinol (5.0 g, 0.0308 mol) and 8.69 g (0.0924 mol) of ethanedithiol were dissolved in 75 ml of glacial acetic acid to which was added 17.46 g (0.123 mol) of boron trifluoride etherate during 15 min. The solution was magnetically stirred at room temperature for 24 hr and the product collected. Five successive filtrations gave more product from the filtrate upon standing. The combined yield was 0.87 g (8%). Recrystallization from 1,2-dichloroethane gave white crystals: mp 287–287.5°; for uv data see Table I; nmr, δ 3.28 H_a, 2.70 H_b.

(3) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Nmr data were recorded on a Varian Associates Model A-60 spectrometer using tetramethylsilane as an internal standard and using tetramethylsilane as an internal standard and using $CDCl_3$ as the solvent. Microanalyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England, and Huffman Microanalytical Laboratories, Wheatridge, Colo.

Anal. Calcd for $C_{12}H_{18}S_6$: C, 40.64; H, 5.12; S, 54.25. Found: C, 40.76; H, 5.04; S, 54.06.

13,13-Dimethyl-1,4,8,11-tetrathiadispiro[4.1.4.3]tetradecane 1,1,4,4,8,8,11,11-Octaoxide.—Trifluoroperoxyacetic acid was prepared by adding trifluoroacetic anhydride (84 ml, 0.398 mol) during 15 min to a stirred, ice-cold solution of 15 ml of chloroform and 14 ml (0.50 mol) of 90% hydrogen peroxide. After 20 min this solution was added during 30 min to a stirred, ice-cold suspension of 2.0 g (0.00684 mol) of 13,13-dimethyl-1,4,8,11-tetrathiadispiro[4.1.4.3]tetradecane, 7 g (0.049 mol) of disodium hydrogen phosphate and 20 ml of chloroform. The slurry was refluxed for 12 hr and poured into 500 ml of ice–water and 100 ml of chloroform. The heterogeneous solution was made neutral with sodium bicarbonate and shaken. Filtration and washing with chloroform and water gave 1.91 g of white microcrystalline 13,13-dimethyl-1,4,8,11-tetrathiadispiro[4.1.4.3]tetradecane 1,4,4,8,8,11,11-octaoxide (66%), mp 260–280° with sintering. The addition of methanol caused two crystalline modifications having different solvent properties to separate: methanol soluble, mp 230–245° with sintering; methanol insoluble, mp 260–280° with sintering. Their infrared spectra (KBr) were different in the 700–950-cm^{-1} region, but identical at 1125 and 1335 cm^{-1}, indicative of a sulfone.

Anal. Calcd for $C_{12}H_{20}S_4O_8$: C, 34.27; H, 4.79; S, 30.50. Found: C, 34.86; H, 5.09; S, 30.42.

Registry No.—**1**, 177-16-2; **2**, 7490-36-0; **3**, 15856-34-5; **4**, 15732-74-8; **5**, 15814-64-9; **6**, 311-37-5; 13,13-dimethyl-1,4,8,11-tetrathiodiaspiro[4.1.4.3]tetradecene 1,1,4,4,8,8,11,11-octaoxide, 15814-66-1.

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Evaluation of Steric Effects in Additions to Substituted Cyclohexenes[1]

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A number of mono- and dialkylsubstituted cyclohexenes have been prepared and subjected to hydroboration under carefully controlled conditions. The alcohol product distributions, obtained on basic peroxide oxidation of the intermediate alkylborane mixtures, are used to assess the source of the steric effects involved in the addition of borane to the cyclohexenyl systems. It is found that in the 1-substituted 4-*t*-butylcyclohexenes, except the 1,4-di-*t*-butyl compound, there is a preference for addition *cis* to the 4-*t*-butyl group. This is attributed to a more prominent steric effect imposed by the axial 4-hydrogen, the effect of which is greater at the 2 position than at the 1 position, and the axial 5-hydrogen, the effect of which is greater at the 1 position than the 2 position. These steric effects are enhanced on substitution of methyl for hydrogen at these positions or by the use of bulky hydroborating agents. Alkyl groups in the 3 position give rise to direct steric effects, effects due to distortion about C_3, and inductive effects. The anomalous results obtained in the hydroboration of 1,4-di-*t*-butylcyclohexene are attributed to steric effects imposed by specific rotational conformations about the C_1-*t*-butyl carbon bond, an effect which is also present in 1-isopropylcyclohexenyl systems. The results are discussed in terms of the proposed distortion of the 4-*t*-butylcyclohexene system by Rickborn and Lwo, and the applicability of the Garbisch model for additions to substituted cyclohexenes in which torsional angle effects in going to the transition state are considered to be important.

Numerous studies of the addition of a variety of reagents to simple substituted cyclohexenes have been reported in the literature. However, very few exhaustive kinetic and stereochemical studies involving these reactions have been carried out. Kwart and Miller[4] have measured the second-order rate constants for the addition of 2,4-dinitrobenzenesulfenyl chloride to a number of 4-mono- and 4,5-disubstituted cyclohexenes. These authors stated "the effect of the substituents of the 4-monosubstituted cyclohexenes on the rate of addition of 2,4-dinitrobenzenesulfenyl chloride is predominantly electronic in nature."[4] A portion of the data of Kwart and Miller is included in Table I for comparison with the relative rates of other addition reactions.

Rickborn and Lwo[5] have measured the rates and determined the stereochemistry of epoxidation of remotely substituted alkyl cyclohexenes (see Table I). These authors suggest "that the effects of remote alkyl groups are primarily steric rather than inductive in nature." The results for 4-methylcyclohexene were rationalized on the basis of a rate retarding steric effect contributed by the conformation with the *axial* methyl group. In order to explain the results of epoxidation of 4-*t*-butylcyclohexene, Rickborn and Lwo[5] invoked an unspecified distortion of the cyclohexene system by the bulky *t*-butyl group.

Consistent with the observation of Rickborn and Lwo on the stereochemistry of epoxidation of 4-*t*-

TABLE I
RELATIVE RATES OF ADDITIONS TO 4-SUBSTITUTED CYCLOHEXENES

	2,4-Dinitrobenzenesulfenyl chloride 30° [a]	Epoxidation at 25° [b]	Diimide reduction at 80° [c]
	100	100	100
	81.2	81 (53.6% *trans* product)	90[d]
	89.7	94 (39.5% *trans* product)	95

[a] See ref 4. [b] See ref 5. [c] E. W. Garbisch, S. M. Schildkraut, and D. M. Patterson, *J. Amer. Chem. Soc.*, **87**, 2932 (1965). [d] Data derived from the 1-*t*-butylcyclohexene and 1-*t*-butyl-4-methylcyclohexene.

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work (PRF 1225-A1, 3). (b) Taken from the Ph.D. Thesis of F. M. K., University of Notre Dame, 1966. (c) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967.

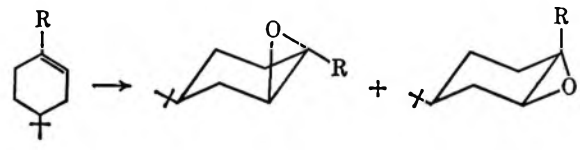
(2) Alfred P. Sloan Research Fellow, 1967–1969.

(3) National Science Foundation Predoctoral Fellow, 1963–1965; Lubrizol Fellow, 1965–1966.

(4) H. Kwart and L. J. Miller, *J. Amer. Chem. Soc.*, **83**, 4552 (1961).

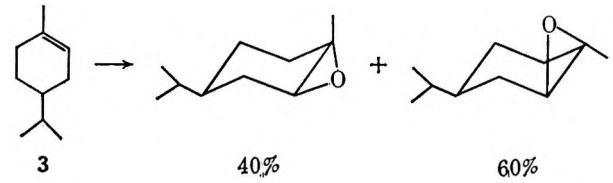
(5) B. Rickborn and S. Y. Lwo, *J. Org. Chem.*, **30**, 2212 (1965).

butylcyclohexene (1), LeBel and Ecke[6] observed that epoxidation of 1-methyl-4-*t*-butylcyclohexene (2) afforded a mixture of the 1-methyl-*trans*- and -*cis*-4-*t*-butylcyclohexene oxides in an approximate ratio of 45:55.

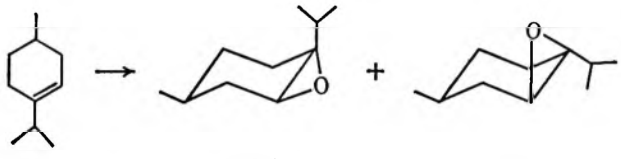


1, R = H	61.5%	39.5%
2, R = CH_3	55%	45%

Bowman and coworkers[7] have investigated the epoxidation of 1- and 3-*p*-menthene with perbenzoic acid. Epoxidation of 1-*p*-menthene (3) yields the 1-methyl-*cis*- and -*trans*-4-isopropylcyclohexene oxides in a 3:2 ratio whereas 3-*p*-methene (4) yields the 1-isopropyl-*cis*- and -*trans*-4-methylcyclohexene oxides in a 2:3 ratio.



3 40% 60%



4 60% 40%

Garbisch and coworkers[8] have investigated the reduction of cyclic, exocyclic, and acyclic olefins with diimide. Based on the assumption that the transition state for diimide reduction probably occurs fairly early along the reaction coordinate, these authors have proposed a model that suggests that the major factors which contribute to the observed reactivity differences are due to torsional strain, bond angle bending strain and α-alkyl substituent effects, with the assumption that steric factors (nonbonded repulsions) involved are likely to be small and hence were ignored. Calculations based on this model predict the relative reactivities of olefins with a remarkable degree of success, usually within a factor of 2.

Garbisch's model as applied to the analysis of the stereochemistry of attack on the cyclohexene ring system is illustrated in Figure 1. Approach of a reagent from side A (*trans* with respect to R″) leads to a reduction of angle τ, thus increasing the eclipsing strain between R and H, and an increase in angle τ' leading to a reduction in the eclipsing strain between R′ and H′. Attack from side B results in opposite changes in τ and τ' and in the eclipsing strain energies. When R = R′ = H, this model does not predict a preference for attack at either side A or B, whereas when R or R′ are more bulky than H, attack would be expected to occur from sides B and A, respectively.

(6) N. A. LeBel and G. G. Ecke, *J. Org. Chem.*, **30**, 4316 (1965).

(7) R. M. Bowman, A. Chambers, and W. R. Jackson, *J. Chem. Soc., Sect. C*, 612 (1966).

(8) See Table I, footnote *c*.

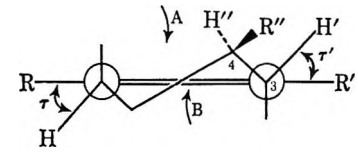


Figure 1.—Garbisch model for additions to substituted cyclohexenes.

The Garbisch model does not adequately explain the stereochemical results of Rickborn and Lwo.[5] The observed trend in the relative rates for epoxidation and diimide reduction[9] of 4-methyl and 4-*t*-butylcyclohexene relative to cyclohexene are not predicted by the Garbisch model although the changes in relative rates are within the sensitivity limits of the calculations.

Discussion

The nature of the steric effects giving rise to the trends observed in the data in Table I are not obvious and cannot be deduced from the reactions described thus far because of the symmetry of the attacking reagent (diimide), the intermediate (episulfonium ion in the addition of 2,4-dinitrobenzenesulfenyl chloride), or the final product (epoxide). In order to assess the steric factors operating in these reactions it is necessary to employ a sterically demanding, unsymmetrical reagent. The addition of borane to an olefin is uniquely well suited for such an investigation. The addition proceeds in a reasonably concerted, *cis* fashion[10,11] and subsequent oxidative work-up with alkaline hydrogen peroxide produces an alcohol in nearly quantitative yield in which the hydroxyl occupies the same site on the carbon atom that was occupied by the boron atom. The analysis of the products of hydroboration reactions can therefore be carried out on the much more easily handled alcohols rather than on the more reactive boranes. Furthermore, the hydroboration reaction has been shown to be quite sensitive to steric factors contained within the olefin[12-14] and the bulk of the hydroborating agent.[15]

In order to evaluate more critically the steric effects generated by remote alkyl groups in substituted cyclohexenes we have undertaken a study of the hydroboration of substituted cyclohexenes. The stereochemical results outlined in this paper are for the reaction of the substituted cyclohexene with an excess of borane in tetrahydrofuran to give predominantly (~95%) the monoalkylborane (see Experimental Section for the details of the analysis). Relativly few examples of the hydroboration of substituted cyclohexenes have been reported in the literature. These

(9) It might be argued that the transition state for epoxidation occurs considerably further along the reaction coordinate and thus the Garbisch model is not applicable. However, the similarity of the relative rates and stereochemistry of additions presented in Table I indicate a considerable degree of similarity exists despite the widely different types of reagents.

(10) H. C. Brown, "Hydroboration," W. A. Benjamin, Inc., New York, N. Y., 1962, p 130.

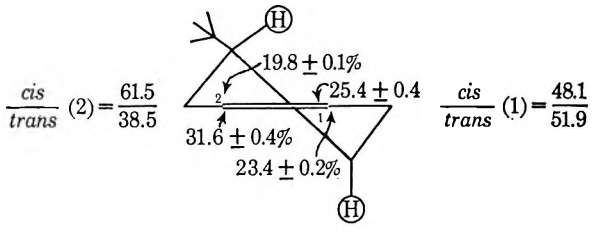
(11) W. G. Woods and P. L. Strong, *J. Amer. Chem. Soc.*, **88**, 4667 (1966).

(12) (a) N. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **29**, 1120 (1964); (b) L. Caglioti, G. Cainelli, G. Marna, and A. Selva, *Tetrahedron*, **20**, 957 (1964); (c) A. Hauser and C. Pillar, *J. Org. Chem.*, **27**, 2914 (1962).

(13) G. Zweifel and H. C. Brown, *J. Amer. Chem. Soc.*, **86**, 393 (1964).

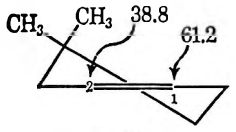
(14) W. Cocker, P. V. R. Shannon, and P. A. Stamland, *Tetrahedron Lett.*, 1409 (1966).

(15) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 3222 (1960); **83**, 1241 (1961).



1

Figure 2.—Positions of attack by boron in the hydroboration of 4-*t*-butylcyclohexene.



7

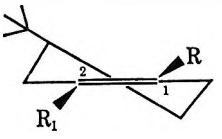
Figure 3.—Positions of attack by boron in the hydroboration of 4,4-dimethylcyclohexene (**7**).

examples will be discussed in the appropriate sections of this article.

Hydroboration of 4-Substituted Cyclohexenes.[16]— The results from the hydroboration of 4-*t*-butylcyclohexene (**1**) are presented in Figure 2; the arrows indicate the position of attack by boron and the percentages indicate the average values for the extent of attack by boron at the indicated positions as determined from several independent experiments. The *cis/trans* ratios (relative to the 4-*t*-butyl group) for attack at the 1 and 2 positions are indicated beside the figure. The over-all *cis/trans* ratio relative to the 4-*t*-butyl group is 55:45, a slight, but nonetheless distinct, favoring of attack *cis* to the 4-*t*-butyl group. Closer inspection of the results presented in Figure 2 reveals that most of the stereochemical discrimination is at position 2. In fact, *trans* is very slightly favored at position 1. These stereochemical results are not predicted by the Garbisch model, and are consistent with the epoxidation results of Rickborn and Lwo[5] who observed a 60.5:39.5 *cis/trans* epoxidation ratio for **1**.

The stereochemical preferences for attack at positions 1 and 2 in **1** are *essentially* identical (within experimental limits) with those observed with 1-methyl-4-*t*-butylcyclohexene (**2**), 1-ethyl-4-*t*-butylcyclohexene (**5**), and 1-methyl-5-*t*-butylcyclohexene (**6**) (see Table II). The *cis/trans* ratios for attack at the 2 position of **2** and **5** are 62.2:37.8 and 64.7:35.2, respectively, compared to 61.5:38.5 for **1**. According to the Garbisch model, addition of borane to **2** and **5** should occur preferentially from the *cis* side (relative to the 4-*t*-butyl group). To this extent the prediction is correct. However, considering the changes in the prediction in going from **1** to **2** and **5**, we might have expected a greater preference for attack *cis* to the *t*-butyl group than observed in going from **1** to **2** and **5** in that the CH_3–H and C_2H_5–H eclipsing interactions in **2** and **5** should be greater than the H–H eclipsing interaction in **1** in which no stereochemical preference is expected. Again, it is interesting to note the similarity in the stereochemical results of hydroboration and epoxidation of **2**, the epoxidation leading to an approximate 55:45 *cis/trans* ratio.[6]

TABLE II
STEREOCHEMISTRY OF ATTACK BY BORANE ON SUBSTITUTED CYCLOHEXENES



Compd	Substituents	*cis*-1/*trans*-1	*cis*-2/*trans*-2
1	R = R_1 = H	48.1/51.9	61.5/38.5
2	R = CH_3; R_1 = H		62.2/37.8
5	R = C_2H_5; R_1 = H		64.7/35.3
6	R = H; R_1 = CH_3	49.3/50.7	

The results of the hydroboration of 1-methyl-5-*t*-butylcyclohexene (**6**) are also presented in Table II. The *cis/trans* ratio for attack at the 1 position in **6** is within experimental limits of the same value for **1**. In the case of **6**, the Garbisch model would have predicted a preference for *trans* addition relative to the 5-*t*-butyl group.

The excellent internal consistency of the results obtained with **1**, **2**, **5**, and **6** indicates that we are dealing with steric effects imposed by the 4-*t*-butylcyclohexenyl system itself, and does not involve steric interactions between the 1- and 2-alkyl groups and adjacent hydrogens on the ring.[17] Inspection of a molecular model of an undistorted half-chair form of 4-*t*-butylcyclohexene does not reveal an obvious basis for rationalizing the over-all *cis/trans* attack ratios. The axial hydrogens on carbons 4 and 5 (circled in Figure 2) might be expected to exert some steric influence on the relative amounts of attack at the 1 and 2 positions on each side of the cyclohexene ring. It therefore appears that Rickborn and Lwo's suggestion of a distorted 4-*t*-butylcyclohexene system[5] is necessary to rationalize the results.

Several distorted cyclohexene systems are conceivable. Such possibilities include a boat conformation and a pseudo-half-chair or "sofa" conformation. Thermodynamic calculations indicate that the boat conformation is less stable than the chair conformation by 2.7 kcal/mol,[18] and that the "sofa" conformation is less stable than the chair conformation by 1.2 kcal/mol.[19] Thus neither of these forms seems reasonable for the present system. A more reasonable possibility is that the bulky *t*-butyl group sterically interacts with the methine hydrogen attached to C_4 causing a distortion of the bond angles about C_4. This type of distortion is similar to the "*gem*-dialkyl" effect of Thorpe and Ingold[20] although in this case the

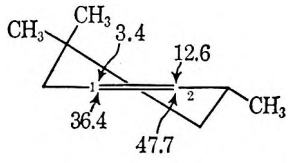
(16) Subsequent to the completion of this study, J. Klein, E. Dunkelblum, and D. Avrahami [*J. Org. Chem.*, **32**, 935 (1967)] reported the results of the hydroboration of 4-methylcyclohexene which gave a mixture of *cis*-3- (28%), *trans*-3- (27%), *cis*-4- (20%), and *trans*-4-methylcyclohexyl alcohol (25%). This product distribution does not correlate well with the steric model developed in this paper. However, the product analysis is very difficult, requiring a partial separation of the alcohols followed by oxidation to the corresponding ketones for analysis, and the figures given might well suffer in accuracy from the procedure used in the analysis. We also attempted to analyze the products derived from the hydroboration of 4-methylcyclohexene but were never completely successful.

(17) It is interesting to note that the similarity of the results obtained from **1**, **2**, **5**, and **6** also indicates that the transition states for the addition of borane to the di- and trisubstituted double bonds must be quite similar, otherwise greater stereochemical preferences should be evident due to different degrees of rehybridization of carbons 1 and 2 in the transition state.

(18) C. W. Beckett, N. K. Freeman, and K. S. Pitzer, *J. Amer. Chem. Soc.*, **70**, 4227 (1948).

(19) R. Bucourt and D. Hainault, *Bull. Soc. Chim. Fr.*, 1366 (1965).

(20) R. M. Beesley, C. K. Ingold, and J. F. Thorpe, *J. Chem. Soc.*, **107**, 1080 (1915); C. K. Ingold, *ibid.*, **119**, 305 (1921). See also E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 197.



8

Figure 4.—Positions of attack by boron in the hydroboration of 3,5,5-trimethylcyclohexene (8).

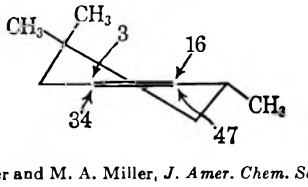
distortion is due mainly to a single, very bulky group. Such a distortion would force the axial C_4 hydrogen (H_{4a}) (see Figure 2) closer to the center of the cyclohexene ring and should then shield the double bond from attack more than its C_5 axial hydrogen (H_{5a}) counterpart. The effect of H_{4a} should be felt more at C_2 than at C_1 owing to the closer proximity of H_{4a} to C_2 than to C_1. Experimentally this is observed with **1** giving rise to a *trans* 2:1 ratio of 44:56. The effect of H_{5a} should be felt more at C_1 than C_2. Again this is experimentally observed with **1** giving rise to a *cis* 1:2 ratio of 43:57.

Substitution of either H_{4a} or H_{5a} by methyl should enhance the steric interaction effects of these positions. Substitution of methyl for H_{4a} does result in a greater preference for attack at the 1 position. For example in the hydroboration of 4,4-dimethylcyclohexene (**7**) the 2:1 ratio is 38.8:61.2 (Figure 3) compared to 43:57 *cis* to H_{4a} in **1**. This value for **7** undoubtedly is not a true reflection of the effect of the 4-axial methyl group in that hydroboration *trans* to this group also occurs, which should favor position 2, thus tending to reduce the apparent effect of the C_4 axial methyl group.

A more informative, but more complex, case is illustrated by the results of the hydroboration of 3,5,5-trimethylcyclohexene (**8**) (see Figure 4).[21] Because of the severe 1,3-diaxial methyl interaction (3.7 kcal/mol in cyclohexane[22]), **8** can be considered as capable of existing essentially only in the conformation illustrated for **8** in Figure 4. The axial 5-methyl group *severely hinders attack cis to itself*, giving a *cis/trans* ratio of 16:84 compared to the corresponding ratio of 45:56 for H_{4a} in **1**. Furthermore, the 2 to 1 position attack ratio *cis* to the axial 4-methyl group in **8** is 21:79 compared to the value of 44:56 in **1**, however there is also an increase in the extent of attack at position 1 *trans* to the axial-5 methyl group. This is not consistent solely with the steric effects outlined in the foregoing paragraphs. It appears that the 3-methyl group is exerting an inductive effect which leads to increased attack by boron at C_2. Evidence in support of this idea is derived from the hydroboration results of 3-methylcyclohexene (see later discussion).

Increasing the steric bulk of the attacking borane is reflected in increased steric interactions with groups

(21) Klein and coworkers have also examined the product distribution derived from the hydroboration of **7** (see ref 16). Their results are illustrated below and agree quite favorably with our results.



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

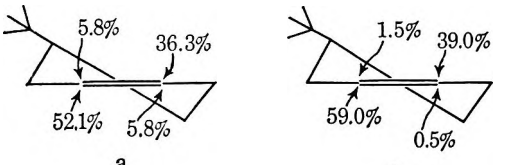
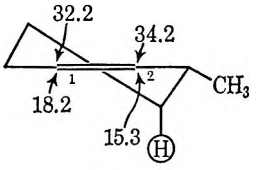


Figure 5.—Positions of attack by boron in the hydroboration of 4-*t*-butylcyclohexene with 2,3-dimethyl-2-butylborane (**a**) and *t*-butylcyclohexylborane (**b**).

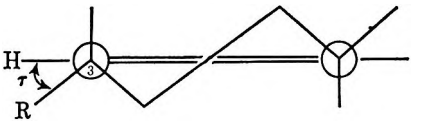


9

Figure 6.—Position of attack of boron in the hydroboration of 3-methylcyclohexene.

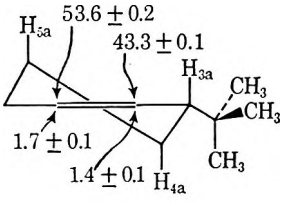
in the 4 and 5 axial positions. Hydroboration of **1** by 2,3-dimethyl-2-butylborane (thexylborane[23]) resulted in a rather slow reaction to give the isomer distribution indicated in Figure 5a. The *cis/trans* ratio has increased slightly (57.9:42.1) relative to the hydroboration of **1** with borane (55:45), however the discrimination between the 1 and 2 positions has increased dramatically (compare with Figure 2). Hydroboration of 1 in a 2:1 olefin–borane ratio resulted in a rather slow formation of dialkylborane. The isomer distribution percentages presented in Figure 5b were determined by quenching the hydroboration reaction mixture with methanol, analyzing the amount of mono- and dialkylboron derivatives present by ^{11}B magnetic resonance followed by correcting the gross isomer distribution values for the amount of product formed by hydroboration of **1** to the monoalkyl stage (from Figure 2). In this instance a greater selectivity is observed than with 2,3-dimethyl-2-butylborane.

Hyroboration of 3-Alkylcyclohexenes.—The torsional angle effect model for additions to 3-alkylcyclohexenes would lead to the prediction that attack *trans* to the 3-alkyl group would be disfavored on the basis of eclipsing strain energies induced by changes in the angle τ. The results for the hydroboration of 3-methylcyclohexene (**9**) are presented in Figure 6.



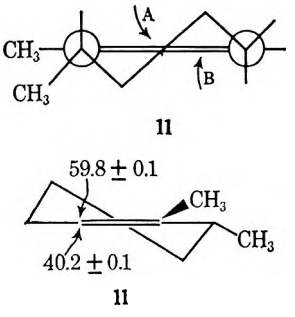
These results are not in agreement with the torsional angle affect model prediction but are more consistent with a direct steric effect by the alkyl group. The interpretation of the results obtained with **9** is difficult owing to the possible existence of two conformations for **9** with the methyl in pseudo-axial or pseudo-equatorial positions. Talaty and Russell[24] have calculated a $-\Delta G$ value for the methyl in the cyclohexenyl system of 0.49 kcal/mol corresponding to approximately 29% of the pseudo-axial conformer at 0°. As we have no measure of the relative rates of hydroboration *cis*

(23) H. C. Brown and G. Zweifel, *ibid.*, **85**, 2066 (1963).
(24) E. R. Talaty and G. A. Russell, *ibid.*, **87**, 4867 (1965).



10

Figure 7.—Positions of attack by boron in the hydroboration of 3-*t*-butylcyclohexene in the most favorable conformation.



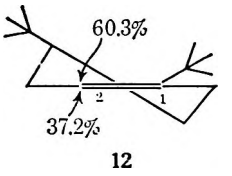
11

Figure 8.—Positions of attack by boron in the hydroboration of 1,6-dimethylcyclohexene.

and *trans* relative to the methyl group in the two conformations further interpretation of the results is not possible.

A further interesting observation can be made regarding the results given in Figure 6. The ratio of attack at the 1 and 2 positions (54:46) relative to H_{4a} (circled in Figure 6) *cis* to the methyl group is slightly less than the similar ratio in **1** (57:43) despite the added steric effect of the methyl group. This observation can be explained by invoking an inductive effect by the 3-methyl group resulting in a greater extent of attack by boron at C_2.[25] A similar effect is noted in Figure 4 for the attack at positions 1 and 2 *trans* to the *axial* 5-methyl group.

The results of the hydroboration of 3-*t*-butylcyclohexene (**10**) are given in Figure 7. 3-*t*-Butylcyclohexene should be a nearly conformationally homogeneous system, and the conformation that one must consider is that with the *t*-butyl group in a pseudo-equatorial position. The steric effect of H_{5a} is over-weighed by the steric effect of H_{3a} (see Figure 7). The increased steric prominence of H_{3a} in **10** compared to **9** is probably due to bond angle distortions about C_3, forcing H_{3a} into a position capable of shielding attack at C_2, similar to the distortion about C_4 in 4-*t*-butylcyclohexene in which the effect of H_{4a} is greater than that of H_{5a}.



12

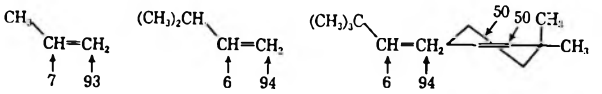
Figure 9.—Positions of attack by boron in the hydroboration of 1,4-di-*t*-butylcyclohexene.

In addition to the steric effects of H_{3a} and H_{5a} in **10** the *t*-butyl group also obviously leads to an additional steric effect shielding the side of the ring *cis* to the *t*-butyl group. This would appear to be due to a preferred rotational conformation of the *t*-butyl group with respect to the substituents bonded to C_3 such that a staggered conformation exists about the C_3-*t*-butyl central carbon atom bond as is illustrated in Figure 7. In this conformation one of the methyl groups of the *t*-butyl group is *syn*-axial producing a severe steric shielding of the side of the ring *cis* to this methyl group (or the *t*-butyl group). The effect of this *syn*-axial-methyl group of the *t*-butyl group appears to be slightly greater than the steric shielding of the pseudo-axial C_5 methyl group in 3,5,5-trimethylcyclohexene. A similar rotational conformational effect must be invoked for the isopropyl and *t*-butyl groups appearing in the 1 position of cyclohexene (see later discussion on the hydroboration of 1,4-di-*t*-butylcyclohexene); however, the *t*-butyl group in the 4 position is too far away from the site of the reaction to produce a direct steric effect.

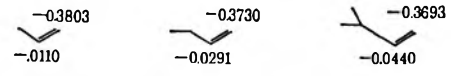
Hydroboration of 1,6-Dimethylcyclohexene.—In a final test of the applicability of the torsional angle affect model, we prepared 1,6-dimethylcyclohexene (**11**) and subjected it to hydroboration. Owing to the CH_3–CH_3 eclipsing strain developed by attack at side A of **11**, the torsional angle affect model would predict that attack would peferentially occur from side B. Experimentally, attack at side A is observed to predominate (see Figure 8). The *cis*/*trans* attack ratio, relative to the 6-methyl group, of 40.2:59.8 in **11** compares favorably with the *cis*/*trans* attack ratio at position 1 in **9** (36.2:63.8) indicating that the predominant factor operating in **11** is the steric effect of the 6-methyl group in the two conformations which are possible.

Hydroboration of 1,4-Di-*t*-butylcyclohexene.—Of the systems studied in the present work, only the results of the hydroboration of 1,4-di-*t*-butylcyclohexene[26] (**12**) (see Figure 9) are not in accord with our steric model or the Garbisch model. The introduction of a 1-*t*-butyl group in place of hydrogen or ethyl, in **1** and **5**, respectively, should not alter the conformation of the cyclohexene ring system and hence the effects of the 4-*t*-butylcyclohexenyl system. The effect produced by the 1-*t*-butyl group must be a consequence of extracyclic conformational steric effects produced by this group.

(25) Similar results have been obtained with acyclic olefins. As one increases the size of the alkyl group bonded to ethylene very little change in the direction of addition of borane is noted (see ref 10, pp 114 and 117). Furthermore, hydroboration of 3,3-dimethylcyclohexene leads to an equivalent extent of introduction of boron to both positions: H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 2544 (1961).



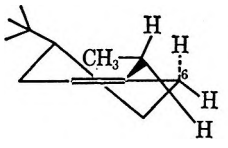
Theoretical support for the presence of an inductive effect is provided by extended Hückel calculations: R. Hoffmann, *J. Chem. Phys.*, **39**, 1397 (1963). As Δ_{12} (difference in charge density between C_1 and C_2 of the olefins) decreases, the discrimination in attack (assuming that the transition



state occurs early along the reaction coordinate such that the transition state highly resembles the ground state) should also diminish. Comparison of the observed hydroboranion results with the calculations indicates that in the simple acyclic olefins the steric, favoring terminal product, and inductive effects, favoring internal product, effectively cancel.

(26) D. J. Pasto and F. M. Klein, *Tetrahedron Lett.*, 963 (1967).

Conformational studies of 1-butene[27] have indicated that the preferred conformations involve eclipsing of the methylene C–H and C–CH_3 bond with the double bond. Incorporating the preferred 1-butene conformations in the structure of 1-ethyl-4-*t*-butylcyclohexene (**5**) gives conformations **13** and **14** (a third conformation is possible similar to **14** in which the methyl group is eclipsed with the other C_6 hydrogen). The



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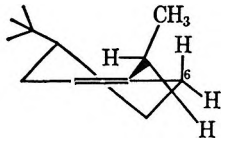
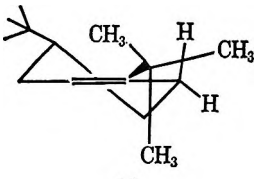


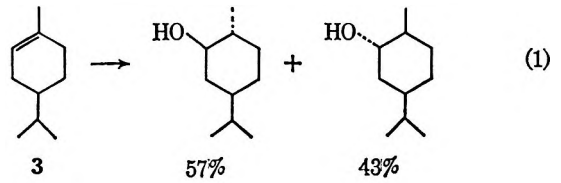
14

C–H bonds of C_6 are positioned such that severe eclipsing between the methylene C–H and methyl bonds of the ethyl group occurs. As the eclipsing strain energy is least in **13**, compound **13** should be the preferred conformation. In this conformation the ethyl group does not offer steric resistance to attack at either side of the cyclohexene ring and hence the results obtained with **5** should be the same as obtained with the parent system (**1**) or the 1-methyl derivative (**2**). With 1,4-di-*t*-butylcyclohexene, however, maintaining eclipsing of one of the methyl groups with the double bond produces two CH_3–H eclipsing interactions with C_6. A slight rotation about the C_1-*t*-butyl carbon bond relieves the two severe CH_3–H eclipsing interactions, and, in what appears to be the most favorable rotational conformation, places one of the *t*-butyl methyls *syn*-axial, *cis* to the 4-*t*-butyl group (see **15**) giving rise to a substantial steric shielding of that side of the cyclohexene ring. The magnitude of this steric effect is quite large; **12** gives only a monoalkylborane in a relatively slow reaction and does not react with 2,3-dimethyl-2-butylborane.



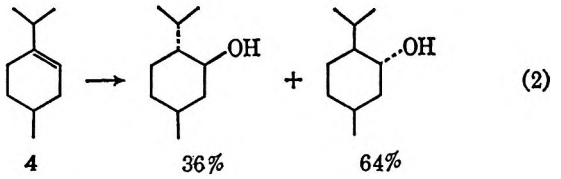
15

Although we were not successful in preparing 1-isopropyl-4-*t*-butylcyclohexene, the steric effects of the group in the 1 position can be inferred from the work of Shumway and Barnhurst[28] and Katsuhara and coworkers[29] which is illustrated in eq 1 and 2. It should



(1)

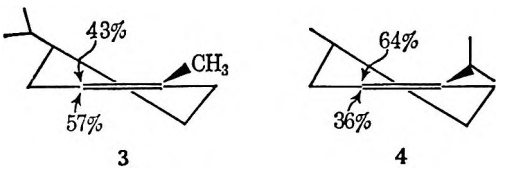
3 57% 43%



(2)

4 36% 64%

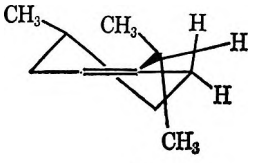
(27) A. A. Bothner-By, C. Naar-Colin, and H. Gunther, *J. Amer. Chem. Soc.*, **84**, 2748 (1962).



3 **4**

Figure 10.—Positions of attack by boron in the hydroboration of 1-*p*-menthene (**3**) and 3-*p*-menthene (**4**).

be noted that the hydroboration of **3** is consistent with our ring substituent steric effect model, involving a slight distortion about C_4 caused by the isopropyl group, and that the hydroboration of **4** is not consistent with this model but compares favorably with the results obtained with 1,4-di-*t*-butylcyclohexene. (One should also note that the stereochemical results for the hydroboration of **3** and **4** almost exactly parallel the epoxidation stereochemistry results with **3** and **4**.[7] This indicates the operation of similar steric effects in both reactions.) The results derived with **4** (see Figure 10) may be explained on the basis of a rotational conformational effect with **16** being the most favorable rotational conformation providing steric hindrance to attack at the double bond *cis* to the 4-methyl group.



16

The results presented in this paper indicate that in the hydroboration reaction steric factors imposed by remote functional groups play the predominant role in determining the stereochemistry of attack on the olefin, and that torsional angle effects as predicted by the Garbisch model are not important. This directly implies that very little rehybridization of the sp^2 olefinic carbon atoms has occurred in the transition state and hence the transition state for the hydroboration reaction must occur very early along the reaction coordinate.

Comparison of the kinetic and stereochemical data for the diimide reduction and epoxidation of these same olefins would indicate that the stereochemistry of attack on these olefins is also controlled by steric effects of remote functional groups and not by torsional angle effects.

Experimental Section

Preparation of Olefins. **4-*t*-Butylcyclohexene** was obtained from Professor E. L. Eliel's research group.

1-Methyl-4-*t*-butylcyclohexene was prepared following the procedure of DePuy and King[30] involving the addition of methylmagnesium iodide to 4-*t*-butylcyclohexanone followed by dehydration with iodine.

1-Ethyl-4-*t*-butylcyclohexene.—This compound, prepared from 10 g (0.065 mol) of 4-*t*-butylcyclohexanone on treatment with 0.07 mol of ethylmagnesium iodide, was dehydrated by distillation from 1 g of iodine. The distillate was dissolved in 150 ml of hexene and flushed successively through 20 × 15 cm Woelm activity II alumina and 21 × 2 cm Fluorisil columns.

(28) D. K. Shumway and J. D. Barnhurst, *J. Org. Chem.*, **29**, 2320 (1964).

(29) J. Katsuhara, H. Wanatabe, K. Hashimota, and M. Kobayashi, *Bull. Chem. Soc. Jap.*, **39**, 617 (1966).

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

Final purification by distillation provided 8 g (74%) of 1-ethyl-4-*t*-butylcyclohexene, bp 75° (15 mm).

Anal. Calcd for $C_{12}H_{22}$: C, 86.67; H, 13.33. Found: C, 86.64; H, 13.25.

1,4-Di-*t*-butylcyclohexene was prepared by the procedure of Stolow and Ward.[31]

1-Methyl-5-*t*-butylcylohexene.—A solution of 20 g (0.12 mol) of 4-*t*-butyl-*o*-cresol (Aldrich Chemical Corp.) in 100 ml of glacial acetic acid was hydrogenated at room temperature on a Parr apparatus in the presence of 1 g of platinum oxide at an initial hydrogen pressure of 50 psi. The theoretical amount of hydrogen was taken up in 4 hr. The solution was poured into 150 ml of water and was extracted three times with 70-ml portions of ether. The combined ether extract was washed three times with 50-ml portions of water, twice with 50-ml portions of saturated sodium bicarbonate solution, and once with 50 ml of 10% hydrochloric acid solution, and dried over anhydrous magnesium sulfate. The solvent was removed on the flask evaporator, giving 17.4 g (84%) of soapy white crystals.

The mixture of isomeric 2-methyl-4-*t*-butylcyclohexanols was dehydrated in the presence of 0.2 go f iodine by refluxing for 5 hr followed by distillation. The olefin mixture was dissolved in 30 ml of pentane, washed with aqueous saturated sodium thiosulfate, dried over magnesium sulfate, and isolated by distillation at 69–80° (19 mm).

Analysis by glpc indicated the mixture contained three components in a ratio of 1:1.5:1.4. A portion of the mixture was separated on a Beckman Megachrom preparative gas chromatograph on a 48 m × 1.5 cm 1,2,3-tris(β-cyanoethoxy)propane column. The latter two fractions thus collected gave nmr spectra consistent with the desired olefin, however the spectra of these two compounds were almost superimposable. Each spectrum displayed singlets at −0.86 (9 H, *t*-butyl) and −1.63 (3 H, methyl), and a broad adsorption at −5.49 ppm (1 H, vinyl). Decoupling the methyl from the vinyl proton served to sharpen the vinyl peak of each spectrum, but did not reveal sufficient differences between the vinyl peaks to enable distinguishing the isomers. Final distinction between the compounds was made by analysis of their hydroboration products indicating that the second of these two olefins was 1-methyl-5-*t*-butylcyclohexene.

3-Methylcyclohexene was purchased from Aldrich Chemical Co. and was purified by distillation.

3-*t*-Butylcyclohexene.—Under a stream of nitrogen, 25 g (0.13 mol) of cis-2-*t*-butylcyclohexyl acetate (obtained from Professor E. Eliel) was pyrolyzed at 450° by dripping through a 50 cm × 2 cm, glass helices-packed column. The product, collected in Dry Ice–acetone cold traps, was taken up in 30 ml of ether, washed three times with 20-ml portions of water and twice with 15-ml portions of saturated sodium bicarbonate solutions and was dried over anhydrous magnesium sulfate. The solution was filtered, and the solvent was removed on the rotary flash evaporator. Distillation gave 4 g (23%) of a clear, colorless, liquid, bp 55.5–57° (15 mm) (lit.[32] 170.5° (746 mm)). Considerable unreacted acetate was also recovered.

4,4-Dimethylcyclopexene was purchased from Aldrich Chemical Co. and purified by distillation.

3,5,5-Trimethylcyclohexene was prepared according to the procedure of Sneen and Matheny.[33]

A mixture of 50 g (0.36 mol) of isophorone, 56.5 ml of 85% hydrazine hydrate, and 30 g (0.46 mol) of potassium hydroxide pellets was dissolved in 150 ml of ethylene glycol and refluxed for 4.6 hr. The reaction mixture was distilled directly. The organic phase of the distillate was separated from the aqueous phase by decantation, and was distilled from a few small pieces of sodium metal (0.2 g) through a 12-cm Vigreaux column. The material distilling at 120–135° was redistilled at 133–134°, giving 15 g (33%) of a mixture of 70% 2,4,4-trimethylcyclohexene and 30% 3,5,5-trimethylcyclohexene. A portion of this mixture was separated by preparative glpc on a 9.2 m × 0.6 cm adiponitrile column, giving pure 3,5,5-trimethylcyclohexene and 2,4,4-trimethylcyclohexene. The nmr spectrum of the 3,5,5-trimethylcyclohexene agrees with that reported by Sneen and Matheny.[33]

1,6-Dimethylcyclohexene.—To a stirred solution of methyl magnesium iodide in ether, prepared by the addition of 79.5 g (0.56 mol) of methyl iodide to 12.2 g (0.51 g-atom) of magnesium turnings in ether, was added slowly 50 g (0.45 mol) of 2-methylcyclohexanone in 200 ml of dry ether. After addition of the ketone, the mixture was refluxed 16 hr and then hydrolyzed with 100 ml of saturated ammonium chloride solution. The ether layer was decanted and the aqueous phase was extracted three times with 70-ml portions of ether. The combined ether extract was washed with 50 ml of saturated sodium thiosulfate solution, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed on the rotary flash evaporator. The crude product (50 g, 88%) was distilled, bp 65–68° (15 mm) (lit.[34] *cis*-1,2-dimethylcyclohexanol, bp 95.7 (53 mm); *trans*-1,2-dimethylcyclohexanol 86.8° (52 mm)).

To a solution of 6.4 g (0.05 mol) of the product (a mixture of the *cis* and the *trans* isomers) in 30 ml of dimethylaniline at 0° was slowly added 7.1 ml (0.10 mol) of acetyl chloride. After all of the acetyl chloride has been added, the mixture was stirred at room temperature for 1 hr and on a steam bath for 3 hr. The solution was then cooled, poured onto 20 g of ice in 50 ml of 10% hydrochloric acid solution, and extracted three times with 35-ml portions of pentane. The combined pentane extract was washed with 20 ml of 10% hydrochloric acid solution and dried over anhydrous magnesium sulfate. After solvent removal *in vacuo*, 6.35 g (75%) of acetate was isolated.

Under a gentle stream of nitrogen, 12.8 g (0.075 mol) of the acetate was pyrolyzed by dropping slowly through a 2 cm × 50 cm glass helices packed column heated to 450°, collecting the effluent from the bottom of the column in Dry Ice–acetone traps. The product was poured into 20 ml of water and extracted with 60 ml of ether. The ether solution was washed twice with 20 ml of water, once with 20 ml of saturated sodium bicarbonate solution, and once with 20 ml of saturated sodium chloride solution, and dried over anhydrous magnesum sulfate. After removal of the solvent, the residue was distilled at 124–136° (750 mm) (lit.[34] 1,6-dimethylcyclohexene, bp 130.3–130.7° (745 mm); 1,2-dimethylcyclohexene, bp 136.2° (745 mm); 2-methylmethylenecyclohexane, bp 124.5 (745 mm)). Analysis by glpc showed this to be a mixture of approximately equal amounts of three components. Based on the results of Froemsdorf, *et al.*,[35] these components are assigned the structures of 2-methylmethylenecyclohexane, 1,2-dimethylcyclohexene, and 1,6-dimethylcyclohexene. The lack of adequate resolution impeded separation in large amounts. The mixture of olefins was used directly in the hydroboration studies in that only 1,6-dimethylcyclohexene is capable of giving rise to the isomeric 2,3-dimethylcyclohexanols, the products required for the desired stereochemical analysis.

Preparation of Compounds for Use as Glpc Standards. 3- and 4-*t*-Butylcyclohexyl Acetates.—Direct analysis of a mixture of 3- and 4-*t*-butylcyclohexyl alcohols (obtained from Professor E. Eliel) could not be accomplished by our available glpc techniques. The alcohols (0.2 g) were converted into the corresponding acetates by treatment with acetic anhydride (1 g) and pyridine (0.25 g). The pure acetates were isolated by pouring the reaction mixture into 10 ml of cold water and extraction with ether. The ether extracts were washed with 10% hydrochloric acid and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residues were purified by distillation in a micromolecular still. The pure acetates were used to determine the relative response ratios.

The crude alcohol mixtures from the hydroboration of 4-*t*-butylcyclohexene were treated with a tenfold excess of acetic anhydride and pyridine in ethereal solution and aliquots of this solution were analyzed directly by glpc. The quantitiveness of the procedure was demonstrated by acetylating a known mixture of the *cis*- and *trans*-3- and -4-*t*-butylcyclohexyl alcohols followed by glpc analysis and comparison of the results with the starting composition.

2-Methyl-5-*t*-butylcyclohexanols were obtained as a mixture of the isomers after hydroboration of 1-methyl-4-*t*-butylcyclohexene. Preparative separation of the two isomers by column chromatography or glpc could not be achieved.

The mixture of isomers was distilled, bp 60° (0.7 mm), and analyzed by nmr. Two peaks appear in the carbinol region of the spectrum, a broad peak at −3.07 ppm (axial carbinol proton) and a sharper peak at −3.79 ppm (equatorial carbinol proton). Planimeter integration of these two peaks gave the ratio of the

(31) R. B. Stolow and J. A. Ward, *J. Org. Chem.*, **31**, 964 (1966).

(32) H. L. Goering, R. S. Reeves, and H. H. Espy, *J. Amer. Chem. Soc.*, **78**, 4926 (1956).

(33) R. A. Sneen and N. P. Matheny, *ibid.*, **86**, 5503 (1964).

(34) T. D. Nevitt and G. S. Hammond, *ibid.*, **76**, 4124 (1954).

(35) D. H. Froemsdorf, C. H. Collins, G. S. Hammond, and C. H. DePuy, *ibid.*, **81**, 643 (1959).

alcohols in this mixture. This known ratio was then used in calculating the response ratio for glpc analysis.

Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 76.96; H, 13.32.

2-Ethyl-5-*t*-butylcyclohexanols were obtained as a mixture of the isomers upon hydroboration of 1-ethyl-4-*t*-butylcyclohexene. Separation of the isomers by column chromatography or glpc could not be achieved.

The mixture of isomers was distilled on a microdistillation apparatus, bp 100° (12 mm). The nmr spectrum of the mixture shows two peaks in the carbinol region, one at −3.07 ppm, assigned to the axial proton, and at −3.82 ppm, assigned to the equatorial proton. As these isomers could not be separated by glpc, the analysis had to be carried out by nmr, comparing the areas of the two carbinol proton peaks mentioned above.

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.45; H, 13.13.

2,5-Di-*t*-Butylcyclohexanols.—The separation, identification and analysis of the 2,5-di-*t*-butylcyclohexanols has been described separately.[26]

***trans*-2-Methyl-*cis*-4-*t*-butylcyclohexanol and *trans*-2-methyl-*trans*-4-*t*-4-*t*-butylcyclohexanol** were obtained from Professor Jiri Sicher.

***cis*- and *trans*-3- and *cis*- and *trans*-2-*t*-butylcyclohexanols** were obtained from Professor E. L. Eliel.

4,4-Dimethylcyclohexanol.—A mixture of 15 ml of Dowex 1 × 7.5 cation exchange resin (washed with sodium hydroxide), 10 ml of methanol, 7.2 g (0.1 mol) of isobutyraldehyde, and 7.0 g (0.1 mol) of methyl vinyl ketone was refluxed for 8 hr with stirring.[36] Distillation of the crude product gave 5.8 g (47%) of 4,4-dimethyl-2-cyclohexen-1-one, bp 92–96 (30–35 mm).

A solution of 4 g (0.032 mol) of 4,4-dimethyl-2-cyclohexen-1-one in 30 ml of glacial acetic acid and 6 ml of concentrated hydrochloric acid was hydrogenated on a Parr apparatus in the presence of 0.2 g of platinum oxide. When 2 molar equiv of hydrogen had been taken up, the sample was removed and poured onto 50 ml of ice and was extracted with four 75-ml portions of ether. The combined extract was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The residue was refluxed for 4 hr with 10 ml of 15% aqueous ethanolic sodium hydroxide, poured onto 20 g of ice, and extracted with two 30-ml portions of ether. The extract was dried over anhydrous magnesium sulfate, and the ether was removed under reduced pressure. The residue was distilled giving pure (by glpc) 4,4-dimethylcyclohexanol, bp 102 (22 mm) (lit.[37] 83.5–83.8 (15 mm).

3,3-Dimethylcyclohexanols was prepared according to the procedure of Doering and Beringer.[38]

3,3- and 4,4-Dimethylcyclohexyl Acetates.—The 3,3- and 4,4-dimethylcyclohexanols were converted into the acetates employing the procedure outlined for the 3- and 4-*t*-butylcyclohexanols to facilitate analysis by glpc.

***cis*-Rich 2,4,4-Trimethylcyclohexanol.**—A mixture of 38 ml of Dowex 1 × 7.5 cation exchange resin (base-washed), 35 ml of methanol, 18 g (0.25 mol) of isobutyraldehyde, and 21 g (0.25 mol) of ethyl vinyl ketone was refluxed with stirring for 19 hr. The solution was poured into 550 ml of water and was extracted with 100 ml of ether. The aqueous phase was saturated with sodium chloride and was extracted with ether. The combined ether extract was washed with 25 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and concentrated on the rotary flash evaporator. Distillation through a 50-cm spinning band column afforded 2.58 g (7.5%) of 2,4,4-trimethyl-2-cyclohexen-1-one, bp 79.5 (18 mm) (lit.[39] 190 (760 mm)).

A solution of 6.5 g (0.047 mol) of 2,4,4-trimethyl-2-cyclohexen-1-one in 5 ml of methanol was added to a suspension of 0.3 g of platinum oxide and subjected to hydrogenation with the absorption of 1 equiv of hydrogen. The solution was filtered and the methanol was removed by distillation. Distillation of the product at 70–71° (12 mm) (lit.[40] 87–89° (30 mm)) afforded 5.2 g (75%) of saturated ketone.

The saturated ketone was reduced following the procedure of Eliel and Doyle.[41] A mixture of 5.6 g (0.04 mol) of 2,4,4-trimethylcyclohexanone, 175 ml of 2-propanol, 14 ml of trimethylphosphite, and 50 ml of "Henbest catalyst" [42] was refluxed for 23 hr. The mixture was then stripped of 2-propanol and acetone under reduced pressure, diluted with 200 ml of water, and extracted with three 100-ml portions of ether. The ether extracts were combined, washed with water, and dried over potassium carbonate. After removal of the solvent on the rotary flash evaporator, the residue was distilled at 62° (16 mm) giving 5 g (89%) of alcohol, free of ketone by ir analysis and 95% pure by glpc. The nmr spectrum displays, in addition to the higher field absorption, a slightly broadened peak at −3.76 ppm, attributed to the equatorial carbinol proton, and a very broad, low-intensity absorption at −2.97 ppm due to the carbinol proton of the *trans* isomer, present as a minor impurity (~3% by glpc).

Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.70. Found: C, 75.80; H, 12.76.

***trans*-Rich 2,4,4-Trimethylcyclohexanol.**—An ether solution of 0.5 g (3.6 mmol) of 2,4,4-trimethylcyclohexanone was added to an ether suspension of lithium aluminum hydride and stirred for 1 hr at room temperature. The mixture was hydrolyzed with 10 ml of 10% hydrochloric acid solution and filtered. The ether was separated, washed with 10 ml of 10% hydrochloric acid solution, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed on the rotary flash evaporator, and the residue was distilled on a microdistillation apparatus, bp 60–70° (16 mm) (lit.[43] 192–193° (760 mm)).

Glpc analysis of the product revealed it was a two-component mixture. The minor component (14%) is *cis*-2,4,4-trimethylcyclohexanol, and the major (86%) product is assigned the structure of *trans*-2,4,4-trimethylcyclohexanol. The latter compound was not obtained free of the other isomer. The nmr spectrum of the sample displays a broad peak at −2.97 ppm.

***cis*- and *trans*-3,3,5-trimethylcyclohexanol** were obtained from Professor E. Eliel.

***trans,cis*-Rich 2,3-dimethylcyclohexanol** was prepared according to the procedure of Ulery and Richards.[44]

***trans,trans*-2,3-Dimethylcyclohexanol.**—An attempt to prepare *trans,trans*-2,3-dimethylcyclohexanol by reduction of *cis*-2,3-dimethylcyclohexanone[35] with the "Henbest catalyst"[42] failed, producting instead a mixture containing only *cis,trans*- and *cis,cis*-2,3-dimethylcyclohexanol.[45]

Hydroboration of the Substituted Cyclohexenes.—The substituted cyclohexenes were subjected to hydroboration in tetrahydrofuran at 0° for 30 min employing a 1:2 olefin:borane–tetrahydrofuran ratio. The reaction mixtures were hydrolyzed and oxidized by the addition of a 50% excess of 20% sodium hydroxide and 30% hydrogen peroxide. After stirring at room temperature for 30 min the oxidized reaction mixtures were extracted three to five times with ether. The ether extract was dried over magnesium sulfate and concentrated by distillation employing a short Vigreaux column. The resulting ether solutions were analyzed directly by glpc, except in cases where prior acetylation was necessary, employing Carbowax columns at appropriate temperatures.

The results obtained with the individual olefins are indicated in the results and discussion section. Generally, several runs were made with each olefin, the values given being the average average values with an average deviation of generally less than 0.5%.

Determination of the Extent of Hydroboration.—Aliquots from several of the hydroboration reaction mixtures were removed and quenched with excess methanol. The samples were concentrated under reduced pressure and analyzed by ^{11}B magnetic resonance. All samples tested contained less than 5% dialkyl borinate as indicated by the intensity of the peak at −53 ppm,

(36) E. D. Bergmann and R. Corrett, *J. Org. Chem.*, **23**, 1507 (1958).
(37) E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957).
(38) W. von E. Doering and F. M. Beringer, *ibid.*, **71**, 222 (1949).
(39) K. von Auwers, *Ann.*, **420**, 110 (1919).
(40) M. Yanagita and S. Inayama, *J. Org. Chem.*, **19**, 1724 (1954).
(41) E. L. Eliel and T. W. Doyle, *Org. Syn.*, in press.
(42) A mixture of iridium trichloride, hydrochloric acid and water; *cf.* Y. M. Y. Haddad, H. B. Henbest, J. Hiesbands, and T. P. B. Mitchell, *Proc. Chem. Soc.*, 361 (1964).
(43) O. Wallach and A. Scheunert, *Ann.*, **324**, 106 (1902).
(44) H. E. Ulery and J. H. Richards, *J. Amer. Chem. Soc.*, **86**, 3113 (1964). Details of the modifications may be found in the Ph.D. Dissertation of F.K., University of Notre Dame, 1967.
(45) In view of the fact that the *trans,trans*-2,3-dimethylcyclohexanol could not be obtained in sufficiently pure form in order to determine the required accurate glpc response ratio, a response ratio was used corresponding to other *cis*- and *trans*-3-methylcyclohexanol systems. The error introduced is believed to be less than 5% of the final calculated composition percentages.

relative to boron trifluoride etherate, relative to the alkyl boronate peak at −32 ppm.

Registry No.—1. 2228-98-0; 2, 3419-74-7; 5, 15822-49-8; 6, 15822-50-1; 7, 14072-86-7; 8, 933-12-0; 9, 591-48-0; 10, 14072-87-8; 11, 1759-64-4; 12, 5009-02-9; 2-methyl-5-*t*-butylcyclohexanol, 15822-55-6; 2-ethyl-5-*t*-butylcyclohexanol, 15822-56-7; *cis*-2,4,4-trimethylcyclohexanol, 15822-57-8.

Acknowledgment.—The authors wish to thank Professor E. L. Eliel and J. Sicher for kindly providing many of the compounds required in this investigation.

1,3-Bridged Aromatic Systems. III.[1,2] Ring-Opening Reactions of *gem*-Dihaloacetoxycyclopropanes

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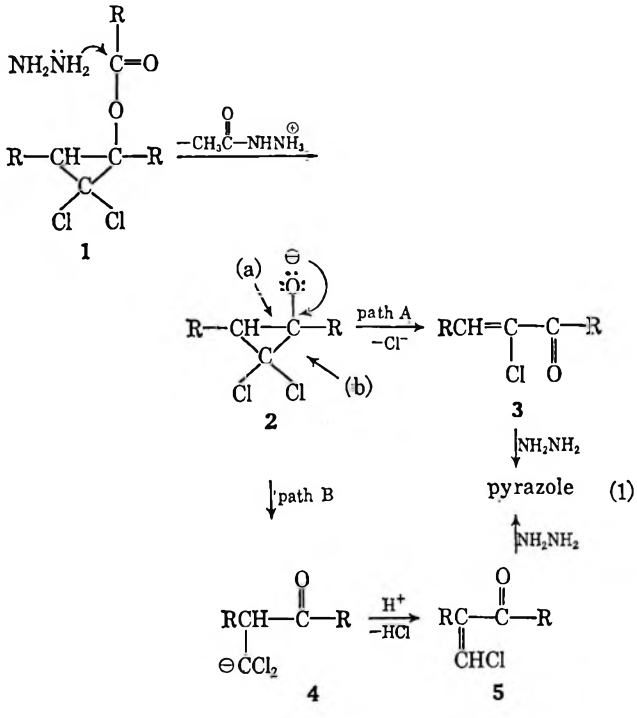
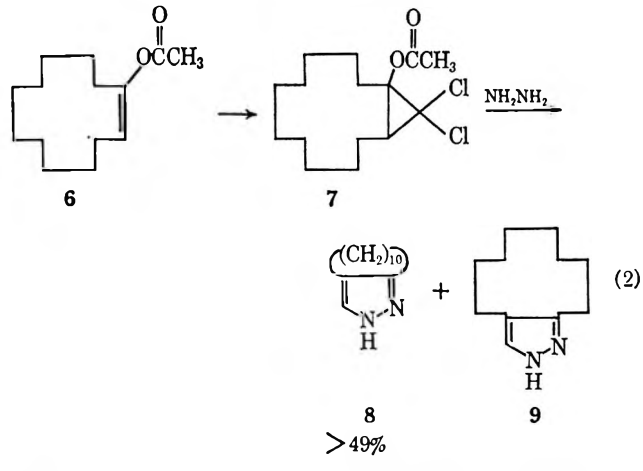
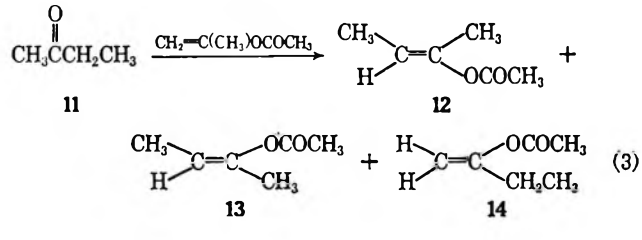
Reactions of hydrazine with dihalocyclopropanes derived from *cis*-2-buten-2-ol acetate, *trans*-2-buten-2-ol acetate, 1-cyclohexenyl acetate, and 1-cyclooctenyl acetate are described. A duality of mechanism is established for such reactions leading, in certain cases, to 3,4- and 3,5-disubstituted pyrazoles. The effect of stereochemistry and the effect of ring size on the course of reaction is considered.

We have previously reported[2a] that the reaction of dichlorocyclopropanes derived from enol acetates with hydrazine constitutes a new and useful synthesis of pyrazoles. Direct evidence for the reaction sequence shown in path A of eq 1 was provided by the observed formation of 3,5-pyrazoles with dichlorocyclopropanes derived from the enol acetates of desoxybenzoin and cyclododecanone. However, the formation of small quantities of the 3,4-substituted pyrazole **9** from **7**, in addition to the 3,5-metacyclophane **8**, suggested that[4] an alternate mechanism, as shown in path B of eq 1, may be operative. A study of the reactions of cyclopropanes **15a**, **15b**, **19b**, and **20** with hydrazine has now provided convincing evidence for the duality of mechanism as shown in eq 1, and the results of this study constitute the subject of this report.





Treatment of butanone (**10**) with isopropenyl acetate (**11**) and *p*-toluenesulfonic acid afforded a mixture[5] of isomeric enol acetates (eq 3) which were separated by preparative vapor phase chromatography. The *cis* isomer **12** was obtained pure; however, **13** and **14** were not completely separated by glpc, and the mixture containing 77% of **13** and 23% of **14** was used in subsequent reactions.



The configurations of **12** and **13** were assigned on the basis of long-range coupling between the protons in the methyl groups, the differences in chemical shift for the β-olefinic protons, and comparison with model compounds. In this case homoallylic coupling between

(1) Supported by the National Science Foundation Grant GP-6169X.

(2) For previous papers in this series, see (a) W. E. Parham and J. F. Dooley, *J. Amer. Chem. Soc.*, **89**, 985 (1967); (b) W. E. Parham and J. K. Rinehart, *ibid.*, **89**, 5668 (1967).

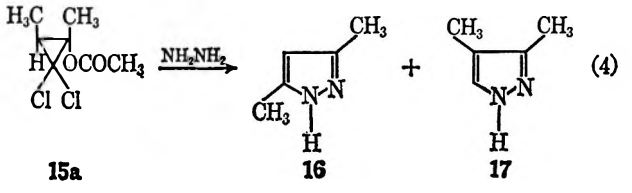
(3) Taken in part from the Ph.D. thesis of J. F. Dooley, University of Minnesota, 1967.

(4) Chloro ketones of type **3** and **5** are known to give 3,5- and 3,4-disubstituted pyrazoles, respectively, by reaction with hydrazine. *Cf.* K. V. Auwers and H. Broche, *Ber.*, **55**, 3880 (1922), and K. W. Auwers and R. Hugel, *J. Prakt. Chem.*, [2] **143**, 157 (1935).

(5) F. G. Young, *J. Amer. Chem. Soc.*, **72**, 3635 (1950).

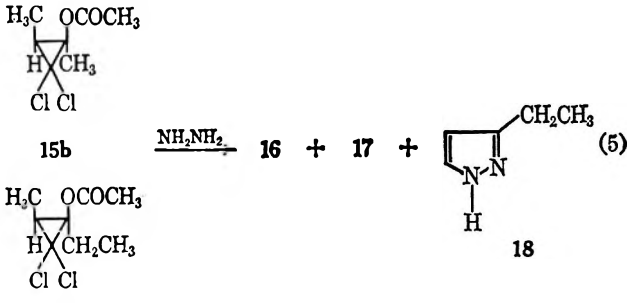
the methyl protons which are separated from one another by five bonds (four single bonds and one double bond) is observed. Numerous reports have shown that the magnitude of $J_{1,4}$ is in the order of 0.5–2.0 cps.[6–8] Furthermore, the magnitude of this coupling is larger when the two methyl groups are *trans*-oriented about the double bond than when they are *cis*-oriented.[9] The observed sizes of $J_{1,4}$ for **12** (1.10 cps) and **13** (1.50 cps) correspond to the assigned configurations. The proton resonance of the *cis*-β-olefinic proton in enol acetates is reported[10,11] to occur downfield from that of the *trans* proton. This observation corresponds to the assigned configurations of **12** and **13**. The nmr spectra of **12** and **13**, together with those of model compounds, are summarized in Table I (Experimental Section).

Reaction of **12** with phenyl(trichloromethyl)mercury in refluxing benzene solution gave *cis*-1-acetoxy-2,2-dichloro-1,3-dimethylcyclopropane (**15a**) in 72% yield. Reaction of **15a** with excess hydrazine gave a mixture of pyrazoles (96% yield) composed of 3,5-dimethylpyrazole, **16** (83%), and 3,4-dimethylpyrazole, **17** (17%). The isolation of these two pyrazoles from this reaction is consistent with the duality of mechanism shown in eq 1. Similarly, treatment of the cyclopropanes derived from the mixture of **13** and **14** with hydrazine gave a mixture of pyrazoles (98% yield) composed of **16** (74%), **17** (5%), and 3-ethylpyrazole, **18** (21%). These results, together with



15a **16** **17** (4)

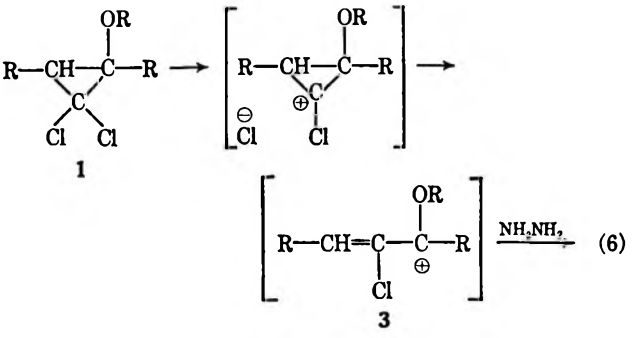
those observed previously[2a] for *trans*-1-acetoxy-2,2-dichloro-1,3-diphenylcyclopropane, suggest a preference for ring opening as shown in path A of eq 1 for *trans*-substituted *gem*-dihaloacetoxycyclopropanes.



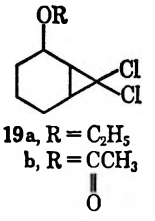
The explanation for this preference is not obvious at this time; however, significant differences in reaction rates for halocyclopropanes with subtle structural variations have been reported previously.[12–14]

(6) J. T. Pinkey and S. Sternkell, *Tetrahedron Lett.*, 275 (1963).
(7) E. B. Whipple, *J. Chem. Phys.*, **35**, 1039 (1961).
(8) A. A. Bothner-By, C. Naar-Colin, and H. Gunther, *J. Amer. Chem. Soc.*, **84**, 2748 (1962).
(9) J. H. Richards and W. F. Beach, *J. Org. Chem.*, **26**, 623 (1961).
(10) J. J. Riehl, J. M. Lenn, and F. Hemmert, *Bull. Soc. Chim. Fr.*, 224 (1963).
(11) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).
(12) L. Skattebøl, *ibid.*, **31**, 1554 (1966).
(13) S. T. Cristol, R. M. Sequevia, and C. H. DePuy, *J. Amer. Chem. Soc.*, **87**, 4007 (1965).
(14) W. E. Parham and R. J. Sperley, *J. Org. Chem.*, **32**, 924 (1967).

An alternative mechanism to those shown in eq 1 for the formation of pyrazoles from acetoxycyclopropanes could involve prior ionization of a carbon–chlorine bond, with subsequent or concerted collapse of the cyclopropyl cation as shown in eq 6.[15,16] A study of the reaction of **19a** and **19b** with hydrazine was made



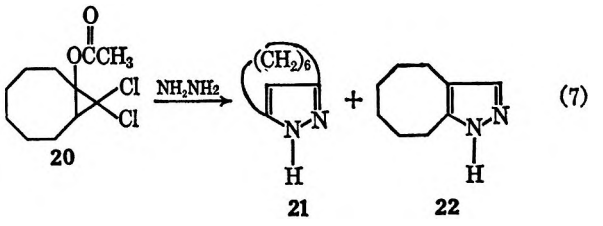
in order to evaluate this reaction sequence. Reaction of **19a** at the O–R function, unlike that of **19b**, cannot occur with hydrazine, since there is no carbonyl group present. On the other hand, if the reaction involves prior ionization of the C–Cl bond, then both **19a** and **19b** would be expected to react with hydrazine. As will be discussed subsequently, reaction of **19b** with hydrazine in ethanol was exothermic, and there was no unchanged **19b** after an 8-hr reaction period at the reflux temperature. However, **19a** does not react with hydrazine at an observable rate under these conditions, and was essentially unchanged after 8 hr. These



19a, R = C_2H_5
b, R = CCH_3 (O)

results suggest that pyrazole formation is the result of initial attack of hydrazine at the carbonyl carbon of **1** as shown in eq 1.

In order to examine the effect of ring size on the yield and course of this synthesis, the reaction of cyclopropanes derived from several cyclic enol acetates was studied. Treatment of 1-cyclooctenyl acetate with phenyl(trichloromethyl)mercury gave 1-acetoxy-9,9-dichlorobicyclo[6.1.0]nonane (**20**) in 80% yield. Reaction of **20** with hydrazine gave a mixture of 3,5-[6]-pyrazolophane (**21**) and 2H-cyclooctapyrazole (**22**) in an

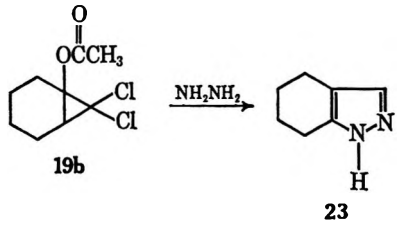


over-all yield of 55% (eq 7). The isomeric pyrazoles were not separated by vapor phase chromatography, absorption chromatography, or distillation. The relative quantities of each isomer was estimated by the

(15) W. E. Parham, H. E. Reiff, and P. Schwartzentruber, *J. Amer. Chem. Soc.*, **78**, 1437 (1956).
(16) W. E. Parham and E. E. Schweizer, *Org. Reactions*, **13**, 55 (1963).

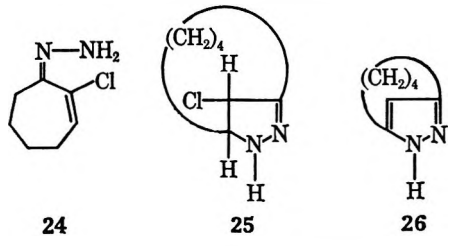
integrated ratio of peak areas of the annular protons in the nmr spectrum of the mixture. On this basis, the over-all yields of isomers were estimated to be 15% of **21** and 40% of **22**. The picrate of the major product **22** was obtained pure and was shown to be identical with an authentic sample.

1-Acetoxy-7,7-dichlorobicyclo[4.1.0]heptane (**19b**) gave 4,5,6,7-tetrahydroindazole (**23**) in 40% yield by reaction with hydrazine (considerable amounts of tarry materials were also formed). Molecular models suggest



19b **23**

that the 3,5 bridge of the planar pyrazole system could accommodate no less than six carbon atoms without severe bending strain. Attempts to detect the presence of **24** or **25** in the product mixture were unsuccessful.



24 **25** **26**

Whether a 3,5- or a 3,4-substituted pyrazole is formed by reaction of cyclopropanes of type **1** (eq 1) with hydrazine is thus seen to be a consequence of whether bond a or bond b is broken in the incipient intermediate **2**. Breaking the bond labeled a can be accompanied by synchronous loss of chloride to yield **3** directly, and appears to be favored. Breaking bond b, on the other hand, gives a carbanion (**4**) which must undergo protonation and elimination. When the two R groups in compound **1** represent a tetramethylene or hexamethylene bridge, reaction path A would lead to a strained seven- or nine-membered ring, and path B appears to be more competitive.

The study of the scope of this synthesis and its extension to other 1,3-bridged aromatic heterocycles is presently under consideration.

Experimental Section[17,18a]

cis- and *trans*-**2-Buten-2-ol Acetate (12 and 13).**—A mixture of *cis*- and *trans*-2-buten-2-ol acetate and 1-buten-2-ol acetate was obtained from 2-butanone as previously described.[5] Preparative gas chromatography[18b] of the mixture [bp 110–120° (760 mm), n^{26}D 1.4065] on a Beckman Megachrom preparative gas chromatograph (24 ft, 2.5 in. o.d., 25% Carbowax 20M on Chromosorb W, 95°) gave pure *cis*-2-buten-2-ol acetate (n^{20}D 1.4172, 4% yield), a pure mixture of (25% yield) of *trans*-2-buten-2-ol acetate (77%) and 1-buten-2-ol acetate (23%), a number of fractions of intermediate composition.

The nmr spectrum of **12** showed peaks for CH_3 (doublet of quartets, τ 8.39, J = 3.5 and 1.1 cps, wt 3), α-CH_3 (quintet, τ 8.20, J = 1.1 cps, wt 3), OCOCH_3 (singlet, τ 8.00, wt 3), and =CH (quartet, τ 4.92, J = 7.0 cps, wt 1).

The nmr spectrum of the mixture of **13** (77%) and **14** (23%) showed peaks for CH_3CH_2 (triplet, τ 8.94, J = 7.0 cps), CH_3—CH_2– (quartet, partially obscured, τ 7.90, $J \sim$ 7.0 cps), B—CH_3 (doublet of quartets, τ 8.55, J = 6.7 and 1.5 cps), CH_3 (quintet, τ 8.20, J = 1.1 cps), OCOCH_3 (singlet, τ 7.93) =CH_2 (triplet, ABX_2 with protons nearly equivalent, τ 5.35, J = 1.0 cps), and =C—H (quartet, τ 5.00, J = 7.0 cps).

The stereochemistry of **12** and **13** was assigned on the basis of magnitude of the homoallylic coupling constants, the chemical shift of the β-olefinic proton of the enol acetate, and comparison with model compounds (see discussion and Table I).

cis-**1-Acetoxy-2,2-dichloro-1,3-dimethylcyclopropane (15a).**—A mixture of *cis*-2-buten-2-ol acetate (5.00 g, 0.040 mol) and phenyl(trichloromethyl)mercury (18.38 g, 0.646 mol, 15% excess) in benzene (50 ml) was stirred at the reflux temperature under dry nitrogen for 48 hr. The mixture was cooled and filtered to give phenylmercuric chloride (13.95 g, 97%). The filtrate was concentrated to give a yellow oil (15.46 g, n^{22}D 1.4825). Distillation of this material gave **15a** [5.89 g, 72%, bp 45° (0.25 mm), n^{22}D 1.4562].

Anal. Calcd for $C_7H_{10}Cl_2O_2$: C, 42.67; H, 5.12; Cl, 35.98. Found: C, 42.74; H, 5.01; Cl, 36.08.

The infrared spectrum of **15a** follows: ν_{CH_3} (2940 cm^{-1}), $\nu_{C=O}$ (1755 cm^{-1}), ν_{CH_3} (1450, 1395, 1385 cm^{-1}), ν_{C-O-C} (1235 and 1198 cm^{-1}), and ν_{C-Cl} (860 cm^{-1}). The nmr spectrum of **15a** follows: CH_3 (doublet, τ 8.78, J = 3.0 cps, wt 1), CH_3 (singlet, τ 8.49, wt 3), cyclopropyl H (quartet, τ 8.45, J = 6.0 cps, wt 1), and OCOCH_3 (singlet, τ 7.96, wt 3).

Reaction of *cis*-**1-Acetoxy-2,2-dichloro-1,3-dimethylcyclopropane (15a) with Hydrazine.**—Hydrazine (95%, 3.62 g, 0.108 mol) dissolved in ethanol (20 ml) was added dropwise to a solution of **15a** (4.71 g, 0.024 mol) in ethanol (20 ml), and the solution was heated at the reflux temperature for 16 hr. Sodium hydroxide (4.32 g) was added, and the mixture heated at the reflux temperature for 1 hr. The mixture was cooled and extracted with four 50-ml portions of ether. The dry ($MgSO_4$) extract was concentrated (rotary evaporator) to give 2.20 g (96% yield) of a mixture of 3,5-dimethylpyrazole and 3,4-dimethylpyrazole as a white crystalline solid, mp 75–86°.

The nmr spectrum of the product showed the following absorptions: CH_3 (singlet, τ 8.07), CH_3 (singlet, τ 7.83), CH_3 (singlet, τ 7.80), C=CH_3 (singlet, τ 4.35), N—CH= (singlet, τ 2.83). The integrated peak areas of the annular protons were in the ratio of 32:6.5.

Fractional crystallization of the mixture of **16** and **17** from petroleum ether (bp 60–68°) gave 1.32 g (58% yield) of **16** (mp 104.5–105.0°). The pyrazole **16** was identical (melting point, mixture melting point, and infrared spectrum) with an authentic sample of 3,5-dimethylpyrazole prepared (71% yield)[19] from acetylacetone and hydrazine sulfate.

Further crystallization from the mother liquors afforded 0.31 g (14%) of a solid mp 62–75°, which was identified as a mixture of **16** and **17** by thin layer chromatography. The mother liquor was concentrated to give 0.22 g of a red oil, n^{25}D 1.5080, which was identified by thin layer chromatography to be a mixture of **16** and **17**. Preparative thin layer chromatography of this material gave 21 mg of **17**, mp 52–53°. This product was identical (melting point and mixture melting point) with the pyrazole obtained (mp 54–55°) by treatment of 3-hydroxymethylene-2-butanone with hydrazine.[20]

trans-**1-Acetoxy-2,2-dichloro-1,3-dimethylcyclopropane (15b) and 1-Acetoxy-2,2-dichloro-1-ethylcyclopropane (14).**—A mixture of **13** (77%) and **14** (23%) (8.89 g, 0.078 mol) and phenyl(trichloromethyl)mercury (34.00 g, 0.086 mol) in benzene (70 ml) was heated at the reflux temperature for 48 hr. The mixture was cooled and filtered to give phenylmercuric chloride (23.10 g, 86%). The filtrate was concentrated on a rotary evaporator to give 13.3 g of an oil. The oil deposited an additional 3.23 g (12%) of phenylmercuric chloride when allowed to stand at room temperature. The mixture was washed with 50 ml of petroleum ether (bp 60–68°) and filtered. The filtrate was concentrated to give 9.89 g of a yellow oil, n^{25}D 1.4755. Distillation of the

(17) All melting points are corrected.

(18) (a) The nuclear magnetic resonance spectra were obtained at 60 Mc using a Varian Associates Model A-60 spectrometer with 1% tetramethylsilane (TMS) as an internal standard. Unless otherwise stated, all samples were run in dilute carbon tetrachloride solution. (b) We would like to thank Dr. William C. Johnson and Marlen E. Van Overbeke of the Minnesota Mining and Manufacturing Co. for effecting this separation.

(19) R. H. Wiley and P. E. Hexner, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 351.

(20) O. Diels and K. Ilberg, *Ber.*, **49**, 162 (1916).

Table I

Comparison of Nmr Data for *cis*- and *trans*-Enol Acetates

Compound	Substituent α	Substituent β	Substituent β	Substituent X	Chemical shift of β-olefinic proton, Chemical shift	Homoallylic coupling constant ($J_{1,4}$)
12	CH_3	CH_3	H	OAc	4.92	1.10
13	CH_3	CH_3	H	OAc	5.00	1.50
cis-2-Bromo-2-butene[9]	CH_3	CH_3	H	Br		1.12
trans-2-Bromo-2-butene	CH_3	CH_3	H	Br		1.59
cis-1-Heptenolocetate[10]	H	C_5H_{11}	H	OAc	4.76	
trans-1-Heptenol acetate	H	C_5H_{11}	H	OAc	5.32	
cis-1-Propenol acetate[11]	H	CH_3	H	OAc	4.70	
trans-1-Propenol acetate	H	CH_3	H	OAc	5.29	
cis-3-Pentenol acetate[11]	C_2H_5	CH_3	H	OAc	4.87	
trans-3-Pentenol acetate	C_2H_5	CH_3	H	OAc	5.1	

product gave 4.44 g (29%) of a mixture of **15b** and **16**. Vapor phase chromatography of this product [20% Carbowax 20M on Chromosorb W, 80–100 mesh, (100°)/2 min, temp program (100–200°)/10 min] showed only one peak, retention time 11.5 min.

Anal. Calcd for $C_7H_{10}Cl_2O_2$: C, 42.67; H, 5.12; Cl, 35.98. Found: C, 42.77; H, 5.29; Cl, 35.93.

The infrared spectrum of the product follows: $\nu_{cyclopropane}$ (3030 cm^{-1}), ν_{CH_2} (2980 and 2920 cm^{-1}), $\nu_{C=O}$ (1755 cm^{-1}), and ν_{C-O-C} (1235 and 1200 cm^{-1}). The nmr spectrum of the product follows: CH_3 (singlet, τ 8.73), CH_3 (doublet, τ 8.91, J = 3.0 cps), CH_3CH_2 (triplet, τ 8.89, J = 9 cps), CH_3CH_2 (quartet, τ 8.45, J = 5 cps) and $OCOCH_3$ (singlet, τ 8.27 and singlet, τ 7.93).

Reaction of 15b with Hydrazine.—A solution of hydrazine (95%, 0.53 g, 16.4 mmol) in ethanol (10 ml) was added dropwise to a solution of the mixture of **15b** and the dichlorocyclopropane derived from **14** (0.72 g, 3.66 mmol) in ethanol (10 ml). The mixture was heated at the reflux temperature for 24 hr. Sodium hydroxide (0.66 g, 16.40 mmol) in water (10 ml) was added and the solution heated at the reflux temperature for 1 hr. The solution was cooled and extracted with four 25-ml portions of ether. The dried ($MgSO_4$) ether extracts were concentrated on a rotary evaporator to give 0.35 g (98%) of a mixture of **16** (74%), **17** (5%), and **18** (21%). The relative amounts of pyrazoles were estimated from the ratio of the integrated peak areas of the annular protons in the nmr spectrum. The nmr spectrum of the product showed complex splitting in the τ 6–10 portion of the spectrum.[16] The aromatic region of the spectrum showed the following absorptions: **18**, 5 H (doublet, τ 2.80, J = 2 cps) and 4 H (doublet, τ 4.17 J = 2 cps) with equal peak areas; **16**, 4 H (singlet, τ 4.40): **17**, 5 H (singlet, τ 2.90). The chemical shift of the annular proton absorptions were identical with those of authentic samples of **16** and **17**.

Attempted Reaction of 1-Ethoxy-7,7-dichlorobicyclo[4.1.0]-heptane (19a) with Hydrazine.—A solution of[21] **19a** (1.00 g, 4.8 mmol) and pentamethylbenzene (0.50 g), which was used as a reference compound, in ethanol (10 ml), was treated with a solution of hydrazine (95%, 0.69 g, 21.5 mmol) in ethanol (5 ml), and the mixture stirred at 25° for 2 hr. The quantity of **19a** was monitored by vapor phase chromatography (5% silicone oil DC710 on Chromosorb W, 80–100 mesh, 100°) by comparing the relative area of the peaks for **19a** (21.6 min) and pentamethylbenzene (14.4 min). No decrease in the concentration of **19a** could be observed. The mixture was heated at the reflux temperature for 8 hr, but only a small decrease in **19a** was observed.

1-Cyclooctenyl Acetate.—1-Cyclooctenyl acetate [bp 87° (3.3 mm), $n^{28}D$ 1.4688; lit.[22] bp 73° (3.4 mm), $n^{25}D$ 1.4705] was prepared (97% yield) from cyclooctanone as previously described.[22] The nmr spectrum of the product follows: CH_2 (broad, τ 8.20–8.50), $OCOCH_3$ (singlet, τ 7.96). CH_2—C=C (broad, τ 7.50–8.10), =C—H (triplet, τ 4.72, J = 8.0 cps).

1-Acetoxy-9,9-dichlorobicyclo[6.1.0]nonane (20).—1-Cyclooctenyl acetate (16.80 g, 0.10 mol) and phenyl(trichloromethyl)-mercury (51.50 g, 0.13 mol) were stirred in dry benzene (140 ml) under an atmosphere of dry nitrogen at the reflux temperature for 48 hr. The mixture was cooled and filtered to give phenylmercuric chloride (34.32 g, 85%). The filtrate was concentrated on a rotary evaporator to give an orange oil (36.72 g, $n^{25}D$ 1.5118). Distillation of the oil gave **20** [19.98 g, 80%, bp 92–94° (0.10 mm), $n^{24}D$ 1.4945].

Anal. Calcd for $C_{11}H_{16}Cl_2O_2$: C, 52.60; H, 6.43; Cl, 28.23. Found: C, 52.65; H, 6.35; Cl, 28.40.

The infrared spectrum of the product follows: ν_{CH_2} (2910, 2850 cm^{-1}), $\nu_{C=O}$ (1759 cm^{-1}), ν_{CH_2} (1470 and 1370 cm^{-1}), ν_{C-O-C} (1200 cm^{-1}). The nmr spectrum ($CDCl_3$) of **20** follows: CH_2 (broad, τ 8.48) and $OCOCH_3$ (singlet, τ 7.92).

Reaction of 1-Acetoxy-9,9-dichlorobicyclo[6.1.0]nonane (20) with Hydrazine.—A solution of hydrazine (95%, 2.66 g, 0.079 mol) in absolute ethanol (5 ml) was added dropwise to a solution of **20** (6.60 g, 0.026 mol) in absolute ethanol (20 ml), and the mixture heated at the reflux temperature for 2 hr. The mixture was cooled to room temperature and filtered to give hydrazine hydrochloride (1.46 g, 41%, mp 87–90°; lit.[23] mp 89°). A mixture melting point with an authentic sample of hydrazine hydrochloride was undepressed, mp 87–90°. The filtrate was concentrated on a rotary evaporator to give 5.78 g of an orange oil, $n^{25}D$ 1.5159. Chromatography of this product on silica gel gave, after elution with ethyl acetate, a clear oil (2.15 g, 55%, $n^{23}D$ 1.5388) which was subsequently identified as a mixture of **21** and **22**. Distillation of the oil gave a clear viscous liquid [bp 106–107° (0.010 mm), $n^{20}D$ 1.5393]; hydrochloride, mp 189–194°; picrate mp 19.0–130.5°.

Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65. Found: C, 71.79; H, 9.10; N, 18.79.

Anal. Calcd for $C_9H_{15}N_2Cl$: C, 57.90; H, 8.10; N, 15.01; Cl, 18.99. Found: C, 57.70; H, 7.74; N, 14.73; Cl, 19.20.

The infrared spectrum of the oil follows: N–H (3170 cm^{-1}), CH_2 (2920–2840 cm^{-1}), and C=N (1670 cm^{-1}). The ultraviolet spectrum showed $\lambda_{max}^{95\%}$ EtOH 222 mμ (log ϵ 3.6), reported[24] for 3,5-dimethylpyrazole $\lambda_{max}^{95\%}$ 225 mμ (log ϵ 3.8). The mass spectrum of the oil exhibited a molecular ion peak at m/e 150; calcd for $C_9H_{14}N_2$ 150. The nmr spectrum of the product follows: CH_2 (broad, τ 8.60–9.00, wt 8), CH_2—C=C (complex multiplet, τ 7.90–8.30, wt 4), and =C—H (singlet, τ 2.68 and singlet τ 3.67). The composition, **21** (27%) and **22** (73%), was estimated from the ratio of the integrated peak area of the annular protons at 2.68 and τ 3.67.

Although vapor phase chromatography on three different columns did not resolve **21** and **22**, thin layer chromatography of the product on silica gel G (90% ethyl acetate, 10% methylene chloride) showed, after development with iodine, two distinct spots. Fractional crystallization of the picrate (mp 129.0–130.5°), obtained by treatment of the mixed pyrazoles with picric acid, gave pure 2H-cyclooctapyrazole picrate, mp 134–135° [mixture melting point with an authentic sample (mp 133.5–134.5°) was 133.5–134)]. Attempts to obtain the picrate of **21** pure by the crystallization of the mixed picrate were successful.

2H-Cyclooctapyrazole (22).—A solution of hydrazine (95%, 19.84 g, 0.58 mol) in ethanol (100 ml) was added dropwise to a solution of 2-hydroxymethylenecyclooctanone (46.76 g, 0.31 mol) prepared in 74% yield as previously described,[25] dissolved in ethanol (200 ml). The resulting yellow solution was heated

(21) W. E. Parham, R. W. Soeder, J. R. Throckmorton, K. Kuncl, and R. M. Dodson, *J. Amer. Chem. Soc.*, **87**, 321 (1965).

(22) N. J. Leonard and F. H. Owens, *ibid.*, **80**, 6039 (1959).

(23) Physical Constants of Inorganic Compounds, "Handbook of Chemistry and Physics," The Chemical Rubber Co., Vol. 46, Cleveland, Ohio, 1965, p B-179.

(24) A. W. L. Mosby, *J. Chem. Soc.*, 3997 (1957).

at the reflux temperature for 15 hr, and the cooled solution was poured into water (500 ml). The resulting mixture was extracted with three 150-ml portions of ether. The combined ether extracts were dried ($MgSO_4$) and concentrated on a rotary evaporator to give 70.0 g of a clear liquid, $n^{25}D$ 1.4468. Distillation of the liquid gave 2H-cyclooctapyrazole (29.70 g, 64%) as a clear viscous oil [bp 128–129° (0.10 mm), $n^{25}D$ 1.5332]. The oil crystallized upon standing overnight to give a white solid, mp 45°.

Anal. Calcd for $C_9H_{14}N$: C, 71.95; H, 9.39; N, 18.65. Found: C, 71.67; H, 9.33; N, 18.51.

The infrared spectrum of the product follows: ν_{N-H} (3150 cm^{-1}), $\nu_{=CH}$ (3050 cm^{-1}), ν_{CH_2} (2900–2850 cm^{-1}), $\nu_{C=N}$ (1590 and 1575 cm^{-1}). The nmr spectrum of **22** follows: CH_2 (broad, τ 8.53, wt 12), CH_2—C=C (complex multiplet, τ 7.38, wt 4), =C(H)—N (singlet, τ 2.85, wt 1) and N–*H* (broad, τ 3.34, wt 1). The ultraviolet spectrum of **25** showed $\lambda_{max}^{95\% EtOH}$ 222 mμ (ε 13,950).

Crystalline 2H-cyclooctapyrazole picrate (mp 133.5–134.0°) was recovered in 77% yield after treatment of **22** with picric acid solution.

Anal. Calcd for $C_{15}H_{17}N_5O_7$: C, 47.49; H, 4.52; N, 18.46. Found: C, 47.32; H, 4.53; N, 18.19.

1-Acetoxy-7,7-dichlorobicyclo[4.1.0]heptane (19b). **A.**—1-Cyclohexenyl acetate (18.80 g, 0.135 mol) and phenyl(trichloromethyl)mercury (74.95 g, 0.188 mol) were stirred in benzene (200 ml) at the reflux temperature for 48 hr. The reaction mixture was cooled to room temperature and filtered to give phenylmercuric chloride (50.5 g, 86%). The filtrate was concentrated on a rotary evaporator and the residue was distilled to give **19b** [22.56 g, 75%, bp 128–131° (0.80 mm), $n^{25}D$ 1.4892].

Anal. Calcd for $C_9H_{12}Cl_2O_2$: C, 48.45; H, 5.42; Cl, 31.79. Found: C, 48.52; H, 5.43; Cl, 31.43.

The infrared spectrum of the product follows: ν_{CH_3} (2920 and 2850 cm^{-1}), $\nu_{C=O}$ (1755 cm^{-1}), and ν_{C-O-C} (1220 cm^{-1}). The nmr spectrum of **19b** follows: OCOCH_3 (singlet, τ 7.98) and CH_3 (broad, τ 7.50–8.83).

B.—A solution of 1-cyclohexenyl acetate (8.00 g, 0.057 mol) and sodium trichloroacetate (32.50 g, 0.114 mol) in 1,2-dimethoxyethane (125 ml) was heated at the reflux temperature for 5 hr. The solution was concentrated on a rotary evaporator. Distillation of the residue gave **19b** [2.24 g, 18%, bp 93–108° (1.4 mm), $n^{25}D$ 1.4918]. The infrared spectrum of the product was essentially identical with a sample of **19b** prepared as described above.

Reaction of 1-Acetoxy-7,7-dichlorobicyclo[4.1.0]heptane (19b) with Hydrazine.—Hydrazine (95%, 2.72 g, 0.081 mol) dissolved in ethanol (10 ml) was added dropwise with cooling to a solution of **19b** (4.00 g, 0.018 mol) in ethanol (20 ml). The mixture was heated at the reflux temperature for 1 hr, cooled to room temperature, and poured into water (50 ml). The solution was extracted with three 50-ml portions of ether. The dried ($MgSO_4$) ether extracts were concentrated to give 0.68 g of a red oil, $n^{24}D$ 1.5592. The nmr spectrum of the product follows: CH_2 (broad, τ 8.28), CH_2—C=C (complex τ 7.42), and =C—*H* (singlet, τ 2.84). This suggested that the product was impure 4,5,6,7-tetrahydroindazole.

The aqueous layer from the extraction was acidified with 6 *N* HCl solution, and extracted with three 50-ml portions of ether. The dried ($MgSO_4$) ether extracts were concentrated to give 30 mg of black tarry material which was ultimately discarded.

The aqueous layer was adjusted to pH 7 with dilute sodium hydroxide solution and extracted with three 50-ml portions of chloroform. The water layer was saturated with solid potassium carbonate and extracted with 50 ml of chloroform. The combined chloroform extracts were dried ($MgSO_4$) and concentrated to give slightly impure **26** (0.90 g, 41%, mp 65–70°; lit.[25] mp 79.0–79.5°). The nmr spectrum of the product follows: CH_2 and CH_2—C=C (broad, τ 7.4–9.0), =C—*H* (singlet, τ 2.70). The infrared spectrum of the product was essentially identical with that of an authentic sample[21] of **26**, and a mixture melting point of the product with authentic **26** was undepressed.

Registry No.—**12**, 15984-02-8; **13**, 15984-03-9; **15a**, 15984-04-0; **15b**, 15984-05-1; **19b**, 15984-06-2; **20**, 14605-45-9; **21**, 15984-08-4; HCl of **21**, 15984-09-5; **22**, 15984-10-8; HCl of **22**, 15984-11-9; picrate of **22**, 15984-12-0.

(25) C. Ainsworth, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 536.

Alumina-Catalyzed Reactions of Hydroxyarenes and Hydroaromatic Ketones. I. Reactions of 1-Naphthol with Methanol[1a]

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The alumina-catalyzed reactions of 1-naphthol (I) with excess methanol were studied as a function of temperature (275–550°) and catalyst acidity. Three types of reactions were observed: (a) ether formation, (b) ring methylation, and (c) self-condensation of I. Formation of 1-methoxynaphthalene (type a) is significant only at 275–300° over catalysts of low acidity. At 350–550° the predominant reaction (60–95%) is ring methylation with concurrent elimination of the arenolic group to give the following main products (maximal yields of 12–30 mol %): 1,2-dimethylnaphthalene, 1,2,4- and 1,2,7-trimethylnaphthalenes, 1,2,4,7-tetramethylnaphthalene, and 1,2,3,4,6-pentamethylnaphthalene. Smaller amounts of 2-methylnaphthalene, 1,2,3-trimethylnaphthalene, 1,2,3,4-tetramethylnaphthalene, and 1,2,3,4,6,7-hexamethylnaphthalene are also produced. Up to 420° the average depth of methylation was found to increase with increasing acidity of the alumina. Oxygen-containing compounds are formed in yields of 35–60% at 275–300°, but are not found above 420°. They include 2- and 4-methyl-1-naphthols, 2,4-dimethyl-1-naphthol, 1-oxo-2,2-dimethyl-1,2-dihydronaphthalene, and 1-oxo-4,4-dimethyl-1,4-dihydronaphthalene. The preferential methylation of I at C-2 and C-4 observed at 275–300° is in agreement with reactivity indices for the molecule, as calculated by the HMO method. At 470–550° I undergoes some self-condensation to give perylene. Spectral properties of isolated compounds are reported. An unambiguous synthesis of 1,2,4,7-tetramethylnaphthalene was developed.

The alumina-catalyzed reaction of phenol with methanol is employed as a convenient method for the preparation (in 67% yield) of hexamethylbenzene (II).[2] This reaction was first reported by Briner, Plüss, and Paillard,[3] who worked with a flow system mainly at 410–430° and used a large excess of methanol (relative to phenol) in the influent mixture. Compound II was similarly obtained[3] when phenol was replaced with *o*- or *p*-cresol, 3,5- or 4,5-dimethylphenol, or resorcinol. However, benzene did not react with methanol under

(1) (a) This investigation was supported by Research Grants No. CA-5969 from the National Cancer Institute and No. GM 12730 from the National Institute of General Medical Sciences, U. S. Public Health Service. (b) On leave from the Department of Chemistry, Weizmann Institute of Science, Rehovoth, Israel. (c) Research Assistant 1964–1967.

(2) N. M. Cullinane, S. J. Chard, and C. W. C. Dawkins, "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, pp 520, 521.

(3) E. Briner, W. Plüss, and H. Paillard, *Helv. Chim. Acta*, **7**, 1046 (1924).

the same conditions.[4] These results indicate that the phenolic group plays an essential role in the methylation reaction. Cullinane and Chard[5] studied the phenol–methanol reaction at milder temperatures and with nearly equimolar concentrations of the reactants. Low temperatures (200°) favored the formation of anisole, whereas the main products at 345° were *o*- and *p*-cresol, xylenols, and some polymethylphenols plus a small amount of II. It thus appears that the formation of II is a stepwise reaction involving oxygen-containing intermediates. More recently, Landis and Haag[6] reported that the product of the reaction at 400° contains in addition to II, about 9% of pentamethylbenzene. They also claimed that pentamethylbenzene is readily converted into II by reaction with methanol under the same conditions.[7] Briner, *et al.*,[3] and Plüss[8] found that 1- and 2-naphthols (but not naphthalene) react with excess methanol at 420–450° to produce a mixture of alkylnaphthalenes. With the exception of a single tetramethylnaphthalene, however, no individual compounds were isolated from these reactions.

This paper is concerned with a study of the alumina-catalyzed reaction of 1-naphthol (I) with methanol as functions of reaction temperature and catalyst acidity. Since recent studies by Pines, *et al.*,[9] Tung and McIninch,[10] and MacIver, *et al.*,[11] have shown that the direction and/or the rate of alumina-catalyzed reactions are dependent on catalyst acidity, three different types of alumina were used. Catalyst A (sodium-free) was obtained by hydrolysis of purified aluminum isopropoxide. It has been classified as strongly acidic since it shows high activity for the skeletal isomerization of cyclohexene[9] and for the cracking of cumene and 1-hexene above 400°.[10] Catalyst B (Harshaw alumina, containing *ca.* 0.4% sodium) has been classified as weakly acidic since it is effective for the isomerization of 3,3-dimethyl-1-butene to 2,3-dimethylbutenes but is ineffective for isomerizing the latter to 2-methylpentene, or of cyclohexene to methylcyclopentene.[9] Catalyst C (Houdry alumina, containing *ca.* 0.4% sodium) was classified as virtually nonacidic at temperatures below 350° where it showed little effectiveness for the isomerization of 3,3-dimethyl-1-butene.[9] In the present study, however, catalyst C exhibited considerable activity for methylation at 420–550°. Catalysts were preactivated by an identical procedure (see Experimental Section). The crystalline phases present in the three catalysts were reported[9] to be η, γ, and γ plus χ, respectively. Reactions were conducted in nitrogen atmosphere, in a flow system containing a fixed catalyst bed, at several temperatures in the range of 275–550° and with a molar ratio of methanol to 1-naphthol in the influent of 10:1 in most experiments. Products were isolated from the effluent mixtures by preparative gas chromatography and were identified by a combination of infrared and pmr spectral methods, as well as (in many cases) by direct comparison with authentic reference samples. Quantitative analyses of the reaction mixtures were conducted by means of gas chromatography. Data obtained are presented in Table I.

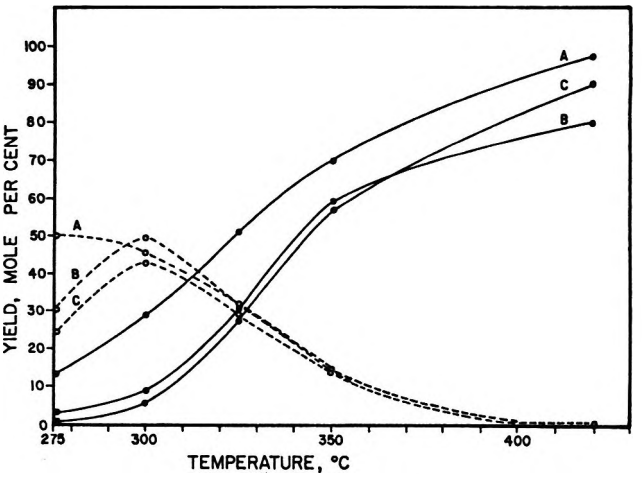


Figure 1.—Relative extents of formation of (a) methyl-substituted naphthols plus oxo compounds (broken curves) and (b) methyl-substituted naphthalenes (continuous curves) over catalysts A, B, and C, as functions of temperature. Data at 325° (not given in Table I) are also included.

Results

As seen from the table there are four types of products formed by the reaction of 1-naphthol with methanol in the range of temperatures studied: naphthyl ethers (III and IV), methylated naphthols (V–VII), methylated oxodihydronaphthalenes (VIII–X), and methylnaphthalenes (XII–XXV). Ether formation is observed in limited yields (up to 16 mol %) only at low temperatures (not >350°). The relative importance of this reaction decreases with increased acidity of the catalyst (*cf.* expt 1–3 and also 4–6, catalyst acidity A > B > C). However, the main reaction at 275–300° is ring methylation (largely, if not entirely, at the 2 and 4 positions) without loss of the oxygen atom from the molecule (see compounds V–X). Smaller amounts of certain methylated naphthalenes (particularly 1,2-dimethyl, 1,2,4-trimethyl, and 1,2,3-trimethyl, in order of decreasing yield) are also produced. As the reaction temperature is increased above 300° the yield of oxygen-containing products falls essentially to zero (attained at *ca.* 420°) whereas the yield of methylnaphthalenes increases rapidly to a maximum of *ca.* 75–95% at 420–470° (see Figure 1). This trend is observed over all of the catalysts, though the maximum yield of oxygen-containing compounds is attained at a lower temperature (possibly <275°) for catalyst A than for the less acidic catalysts B and C. It might be noted that in the low-temperature range (especially at 275–325°) the yield of methylnaphthalenes is also highest with catalyst A. The characteristics of the curves in Figure 1 imply that methyl-substituted naphthols and oxo compounds are probable intermediates in the formation of methylnaphthalenes.

As the reaction temperature is increased from 275 to 550° the composition of the methylnaphthalene product changes. In over-all result the average number of C-methyl groups per naphthalene or hydronaphthalene

(4) A check in our laboratory showed that toluene likewise does not react under similar conditions.

(5) N. M. Cullinane and S. J. Chard, *J. Chem. Soc.*, 821 (1945).

(6) P. S. Landis and W. O. Haag, *J. Org. Chem.*, **28**, 585 (1963).

(7) We have been unable to confirm this claim in our laboratory. Details will be reported in a later paper.

(8) W. Plüss, *Helv. Chem. Acta*, **8**, 507 (1925).

(9) H. Pines and W. O. Haag, *J. Amer. Chem. Soc.*, **82**, 2471, 2488 (1960); **83**, 2847 (1961); H. Pines and C. N. Pillai, *ibid.*, **83**, 2401 (1960); **83**, 3270, 3274 (1961); K. Watanabe, C. N. Pillai, and H. Pines, *ibid.*, **84**, 3934 (1962); H. Pines and J. Manassen, *Advan. Catal.*, **16**, 49 (1966).

(10) S. E. Tung and E. McIninch, *J. Catal.*, **3**, 229 (1964).

(11) D. S. MacIver, W. H. Wilmot, and J. M. Bridges, *ibid.*, **3**, 502 (1964).

TABLE I

COMPOSITION OF PRODUCTS OBTAINED FROM THE ALUMINA-CATALYZED REACTIONS OF 1-NAPHTHOL (I) WITH METHANOL[a]

Experiment no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Catalyst	C	B	A	C	B	A	C	B	A	C	B	A	A	C	B	A	C	B	A
Reaction temp, °C	275	275	275	300	300	300	350	350	350	420	420	420	420	470	470	470	550	550	550
Conversion of I, mol %[b]	37	42	67	66	69	79	75	76	87	~100	85	100	100	100	86	100	100	94	100
Product components,[b,c] mol %																			
1-Methoxy-N (III)	11.0	5.2	2.5	11.7	5.5	2.6	0.7	Trace	...	...	...	...	...	...	...	...	...	...	...
1-Methoxy-2-methyl-N(IV)	0.9	1.5	1.2	4.3	3.5	1.7	0.2	Trace	...	...	...	...	...	...	...	...	...	...	...
2-Methyl-1-naphthol (V)	21.5	27.2	33.2	33.2	37.0	26.5	8.9	10.2	9.6	...	0.7	...	...	...	...	...	...	...	...
4-Methyl-1-naphthol (VI)	0.4	1.3	4.0	2.0	3.8	4.5	1.3	2.1	3.0	...	0.2	...	...	...	...	...	...	...	...
Dimethylnaphthols (VII)[d]	0.1	0.5	1.4	2.3	5.4	0.8	1.0	1.2	0.5	...	0.1	...	...	...	...	...	...	...	...
1-Oxo-2-methyl-1,2-dihydro-N (VIII)[e]	0.2	0.2	0.8	0.3	0.2	1.1	0.6	0.1	0.5	Trace	...	...	...	...	...	...	...	...	...
1-Oxo-2,2-dimethyl-1,2-dihydro-N (IX)	1.9	2.1	7.3	4.9	2.4	8.7	1.5	0.4	0.4	Trace	0.2	0.1	0.1	...	...	...	...	...	...
1-Oxo-4,4-dimethyl-1,4-dihydro-N (X)	...	Trace	2.6	Trace	0.9	3.8	0.6	0.1	0.1	Trace	Trace	...	...	...	...	...	...	...	...
Naphthalene (XI)	...	...	...	...	...	0.1	1.5	0.9	1.5	2.8	1.7	1.3	0.8	3.4	1.8	0.4	1.3	2.6	2.7
1-Methyl-N (XII)	...	...	...	...	...	...	0.8	1.3	1.3	1.6	1.1	1.4	0.9	1.4	1.1	0.6	1.8	2.7	2.7
2-Methyl-N (XIII)	...	...	0.1	0.1	0.1	0.2	3.4	3.4	2.2	3.5	3.1	1.6	1.1	2.6	2.7	1.2	4.7	6.0	6.2
1,2-Dimethyl-N (XIV)	0.5	2.0	7.0	5.1	6.4	16.3	23.1	16.8	18.4	30.0	17.5	19.2	16.4	28.7	18.3	14.9	22.9	14.9	19.5
2,7-Dimethyl-N (XV)	...	...	...	...	...	...	...	...	...	0.3	...	0.3	0.5	...	0.3	1.5	2.9	2.7	3.9
1,2,3-Trimethyl-N (XVI)	...	Trace	1.2	Trace	0.1	3.1	1.8	3.4	5.2	1.9	3.0	4.5	5.4	1.4	2.0	3.0	2.5	2.1	1.8
1,2,4-Trimethyl-N (XVII)	...	1.2	3.5	Trace	2.0	4.2	8.2	6.3	5.0	12.1	6.5	6.8	7.0	11.0	5.8	4.8	8.4	3.6	4.5
1,2,7-Trimethyl-N (XVIII)	...	...	...	...	Trace	Trace	6.3	6.9	7.1	10.3	8.6	12.3	15.5	9.8	8.8	24.8	14.2	9.6	24.0
1,2,3,4-Tetramethyl-N (XIX)	...	Trace	0.3	...	0.1	0.9	1.4	3.9	5.1	4.8	4.3	7.5	2.9	5.9	2.6	2.1	3.5	1.8	1.1
x,x,x,x-Tetramethyl-N (XX)[f]	...	...	0.2	...	0.1	0.6	1.2	3.6	4.5	4.1	3.8	7.2	6.7	3.6	2.7	7.1	5.5	2.8	3.3
1,2,4,7-Tetramethyl-N (XXI)	...	0.1	1.0	...	0.2	2.4	7.1	6.5	7.2	12.5	8.7	12.3	12.2	13.0	6.7	16.4	11.7	4.9	15.7
1,2,3,4,6-Pentamethyl-N (XXII)	...	...	0.1	...	...	0.5	3.1	7.2	10.8	8.0	10.1	17.6	20.0	10.1	5.6	10.3	3.9	2.3	1.1
1,2,3,4,6,7-Hexamethyl-N (XXIII)	...	...	...	...	...	...	...	...	2.0	...	...	4.1	2.6	...	...	1.2	...	...	...
Heptamethyl-N (XXIV)[g]	...	...	...	...	...	...	...	...	...	...	...	Trace	3.8	...	...	Trace	...	...	...
Octamethyl-N (XXV)[g]	...	...	...	...	...	...	...	...	...	...	...	...	1.7	...	...	...	...	...	...
Perylene	...	...	...	...	...	...	...	...	...	...	...	...	...	0.8	0.7	1.0	4.0	3.7	4.8
Unidentified[h]	(0.3)	(0.3)	(0.2)	(1.5)	(1.2)	(1.0)	(3.9)	(3.8)	(2.6)	(8.7)	(15.0)	(3.3)	(1.3)	(5.0)	(26.0)	(6.9)	(2.5)	(29.5)	(2.6)
Depth of ring methylation[i]	0.8	1.0	1.5	1.0	1.2	1.7	2.3	2.7	3.0	2.9	3.0	3.5	3.7	3.3	2.8	3.3	2.6	2.2	2.4

[a] In each experiment (except no. 13) total amounts of starting materials used were 14.4 g (0.1 mol) of I and 32 g (1 mol) of methanol. In run 13 the amount of methanol used was increased to 64 g. [b] Calculated on the basis of 100 mol of starting I (including unreacted material). No quantitative analysis of the side products from methanol, *i.e.*, dimethyl ether, carbon monoxide, and hydrogen,[3] was undertaken. Qualitative tests with a solution of 2,4-dinitrophenylhydrazine showed the presence of small amounts of formaldehyde in the gaseous products above 420°. [c] N = naphthalene. [d] Mainly 2,4-dimethyl-1-naphthol (VIIa). [e] Tentative structure for a product which gave a vpc peak different from V but which was convertible into V by treatment with aqueous sodium hydroxide and then acid. [f] Tentative structure (as based on vpc retention volume and mechanistic considerations[22] only) for 1,2,6,7-tetramethylnaphthalene. [g] Tentative structure, as based on vpc data only. [h] Percentage by weight of total product. For experiments up to 420° these are mainly unidentified chromatographic peaks. Above 420° they are carbon deposits and non-distillable residues. [i] In average number of methyl groups per naphthalene or hydronaphthalene moiety for all identified products (exclusive of recovered I).

ring increases from *ca.* 1 (at 275°) to a maximum of 3–4 (at 420°) and then apparently decreases again. Preferential formation of specific polymethylnaphthalene isomers, particularly 1,2-di-, 1,2,4- and 1,2,7-tri-, 1,2,4,7-tetra-, and 1,2,3,4,6-pentamethyl compounds, occurs. At the same time lesser amounts of naphthalene, the two monomethylnaphthalenes, and the polymethylnaphthalenes with substituents in the 2,7, 1,2,3, 1,2,3,4, 1,2,6,7 (?), and 1,2,3,4,6,7 positions (as well as possible small amounts of hepta- and octamethyl compounds, from run 13 only) are formed. Comparison of this limited array of methylnaphthalenes obtained with the large number of theoretically possible isomers (10, 14, 32, 14, 10 for di, tri-, tetra-, penta-, and hexamethylnaphthalenes, respectively) clearly indicates that an oriented and selective pathway of methylation is involved.

The necessary presence of the arenolic group for effecting ring methylation of I was established by a separate series of experiments in which methanol solutions of 2-methyl-, 1,2-dimethyl-, and 1,2,4-trimethylnaphthalenes were subjected to the same conditions as employed in expt 16. No reaction was observed in any of these experiments. Recovery of starting materials was 92–95%. In another experiment, a portion of the total product mixture from expt 14 was dissolved in methanol (five parts by wt), and the solution was passed over catalyst A at 420°. No change in composition of the product mixture was found. These results also indicate that (at least up to 470°) a methylated naphthalene, once formed, does not isomerize, demethylate, or undergo intermolecular methyl group transfer. It also appears that the high degree of orientation selectivity in the ring-methylation process is ascribable to the influence of the arenolic group.

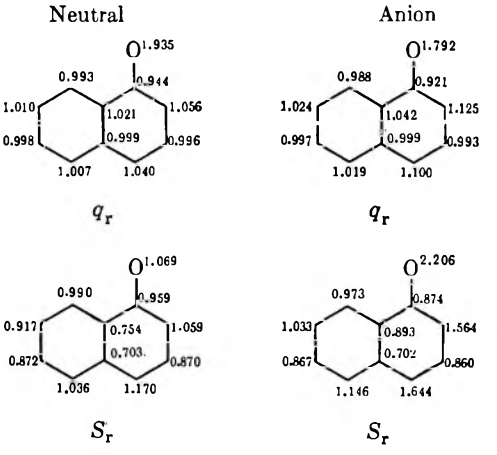
Discussion

It is well known[12] that arenols are more strongly adsorbed on chromatographic alumina than are the corresponding arenes or alkylarenes. With our catalyst the same relative adsorbabilities were found. Thus, the methylated naphthalenes were largely effused from the catalyst bed during the run proper, while residual amounts retained on the catalyst surface were easily desorbed by washing with benzene. On the other hand, unreacted I and its methyl derivatives (V–VII) remained to a large extent adsorbed on the benzene-washed catalyst, from which they could be removed by prolonged extraction with boiling acetone. By analogy with the alumina chemisorption of hydrogen chloride and ammonia the adsorption of I may be vizualized as occurring on acid–base (ion-pair) sites[13] with the proton attached to the basic site and the naphthoxy anion to an adjacent acidic site. Alternatively I may undergo nondissociative adsorption by means of the OH group with resultant weakening of the OH bond.[14] Orientation of the aromatic ring of I on the catalyst surface in the methylation reaction will be considered later.

In Scheme I are presented calculated reactivity indices (π-electron densities, q_r; superdelocalizabilities, S_r) for electrophilic attack at the various positions in I and in 1-naphthoxy anion. Data were obtained by use of simple Hückel molecular orbital theory and the parameters $\alpha_{\ddot{O}} = \alpha_0 + 2.0\beta_0$, $\beta_{C-\ddot{O}} = 0.8\beta_0$ for the neutral molecule[15] and $\alpha_{\ddot{O}} = \alpha_0 + \beta_0$, $\beta_{C-\ddot{O}} = \beta_0$ for the anion. No change in the orders of the indices was observed for small changes in the parameters. One sees that monomethylation should be more facile in the oxygen-bearing ring where attack would be preferred at the oxygen atom and at C-2 and C-4, especially if I is in the ionized form. Substitution into the second ring should be preferred at C-5 and C-7 in the anion, as well as, perhaps, at C-8 in the neutral molecule. Since these calculations do not take into account the entropies of activation for substitution at the various positions, it is to be expected that the data must be modified in order to be of suitably predictive value. Two major entropy factors can be readily visualized. These involve (1) *peri* effects[16] and (2) effects of orientation of the substrate with respect to the catalyst surface. Factor 1 may serve to diminish markedly substitution at C-8 due to the presence of the *peri* oxygen atom at C-1. On the other hand, factor 2 may serve to lower the entropy of activation particularly for substitution at C-2 (and possibly at C-8) if the naphthol molecule or anion were adsorbed in a vertical configuration.[17] If one assumes that the methylating agent is confined to the surface layer, then the observed methylations at C-4, C-6, and C-7 would seem to imply the adsorption of a significant percentage of molecules in a flatwise configuration.[17] On the other hand, the gross predominance of 2-methyl-1-naphthol over that of 4-methyl-1-naphthol at temperatures up to 350° contrasts with the closeness of calculated reactivity indices for the 2 and 4 positions and the known strongly preferential electrophilic attack at C-4 for most reactions occurring in solution.[18] Such preference for 2 substitution in the present reaction might be ascribed either to vertical

SCHEME I

MOLECULAR DIAGRAMS OF 1-NAPHTHOL (NEUTRAL) AND 1-NAPHTHOXY ANION: π-ELECTRON DENSITIES (q_r) AND SUPERDELOCALIZABILITIES FOR ELECTROPHILIC ATTACK (S_r, IN UNITS OF β_0^{-1})



(12) H. H. Strain, "Chromatographic Adsorption Analysis," Interscience Publishers, Inc., New York, N. Y., 1942, pp 14, 15, 92.

(13) J. B. Peri, *J. Phys. Chem.*, **69**, 231 (1965); **70**, 1482, 3168 (1966); B. D. Flockhart, C. Naccache, J. A. N. Scott, and R. C. Pink, *Chem. Commun.*, 238 (1965).

(14) J. R. Jain and C. N. Pillai, *Tetrahedron Lett.*, 675 (1965).

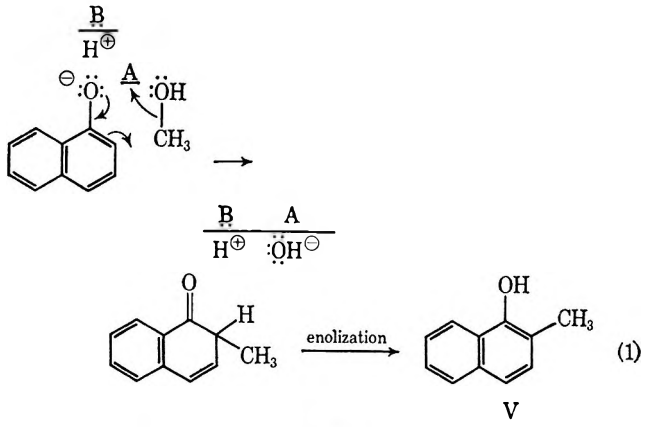
(15) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, pp 117–135.

(16) V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

(17) Compare C. H. Giles, T. H. MacEwan, S. N. Nakhwa, and D. Smith, *J. Chem. Soc.*, 3973 (1960), and L. R. Snyder, *J. Chromatog.*, **16**, 55 (1964), for varying geometries of chromatographic adsorption of phenol.

(18) L. F. Fieser and M. Fieser, "Introduction to Organic Chemistry," D. C. Heath, Boston, Mass., 1957, p 480.

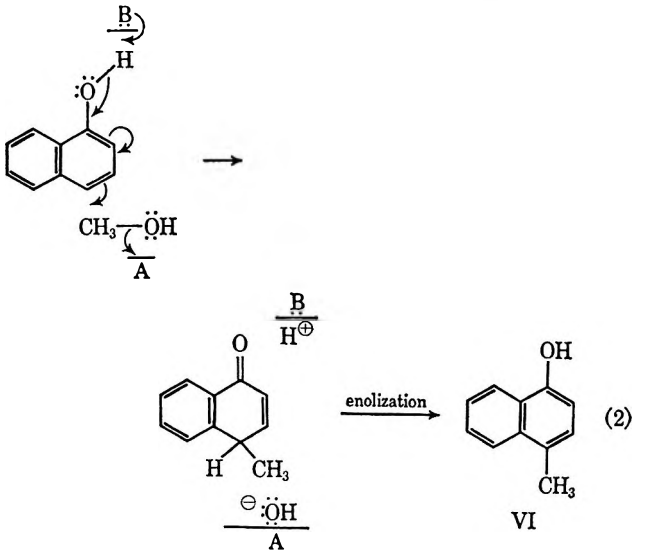
adsorption of I to a major extent or, alternatively, to the intervention of a cyclic transition state involving one molecule of flatwise-adsorbed naphthol, one molecule of methanol, and a single acidic site on the catalyst surface, as shown in eq 1. The latter mechanism for *ortho* methylation would seem to have much in common with the Claisen reaction of alkylating sodium phenoxide with an active halide,[19] the Tiffeneau rearrangement for *ortho* hydroxymethylation of a benzylmagnesium halide with formaldehyde,[19] and the aluminum phenoxide catalyzed *ortho* alkylation of phenols.[20]



(1)

A = acidic site; B = basic site

Although O-methylation of I might be expected to be faster than C-methylation, combined yields of 1-methoxynaphthalene and 1-methoxy-2-methylnaphthalene at 275–300° are much lower than those of 2-methyl-1-naphthol. This result may be due to the reversibility of the O-methylation reaction[5,21,22] and/or to extensive shielding by the catalyst surface of the oxygen atom from attack by the methylating agent. Ring methylation, on the other hand, is essentially irreversible under the same experimental conditions.[23] Although eq 1 has been written for a preliminary ionization step, it may be that the process of ionization is concerted with that of methylation. Either type of mechanism could also serve to give 4-methyl-1-naphthol if A were, instead, located in the proximity of C-4 as shown in eq 2.



(2)

Successive methylation at C-2 and C-4 would give 2,4-dimethyl-1-naphthol; while repeated methylation at either C-2 or C-4 would lead to 1-oxo-2,2-dimethyl-1,2-dihydronaphthalene (IX) or to 1-oxo-4,4-dimethyl-1,4-dihydronaphthalene (X), respectively. The roles of the oxygen-bearing compounds III, V, VI, VIIa, IX, and X as possible intermediates in the formation of methylnaphthalenes were studied separately under reaction conditions. The results and their mechanistic significance are presented in subsequent papers.[22,23] No naphthols or oxodihydronaphthalenes with methyl substituents in the unsubstituted ring of I were isolated. As indicated in later work,[23] however, such intermediates are presumed to be present in the reaction mixture above 300° but to have lifetimes which are too short to allow isolation by our procedure.

The exact nature of the methylating agent has not been established. In eq 1 and 2 adsorption of the methanol to an acidic site on the catalyst is shown as occurring through coordination of a nonbonding electron pair on the alcoholic oxygen.[14] Although it is also indicated that the methylation process is a concerted one, one cannot exclude the possibility of preliminary formation of a methyl carbonium ion. Inasmuch as methanol undergoes dehydrogenation to formaldehyde and carbon monoxide[3] during the reaction and the over-all process of converting a naphthol into a methylated naphthalene involves reduction, one might also consider that formaldehyde or hydroxymethyl carbonium ion ($^{\oplus}CH_2OH$) is the active electrophilic agent.[24] Although no hydroxymethyl compounds were isolated from our reaction mixtures, it is known that hydroxymethylbenzenes are readily converted into methylbenzenes over alumina at 400°.[21]

At 470–550° the reaction mixture contains a significant amount (3.7–4.8 mol per 100 mol of I used, *i.e.*, 7–10% yield) of perylene from condensation of two molecules of I. Also at these high temperatures appreciable carbonization occurs.

The reference compound 1,2,4,7-tetramethylnaphthalene (XXI) was synthesized by an unambiguous method. First Friedel–Crafts succinoylation of toluene[25,26] gave β-(4-methylbenzoyl)propionic acid, converted into its ethyl ester. The position of succinoylation was established by observation of the pmr spectra of these two products, each of which showed only an AB quartet at *ca.* δ 7.5 for the aromatic protons. The ester was then transformed into XXI in an over-all yield of 23% for six steps, one of which produced the known γ-(4-tolyl)valeric acid—free of *meta* isomer[27–29]

(19) C. C. Price, *Org. Reactions*, **3**, 1 (1946).

(20) R. Stroh, R. Seydel, and W. Hahn, "Newer Methods of Preparative Organic Chemistry," Vol. II, W. Foerst, Ed., Academic Press Inc., New York, N. Y., 1963, pp 337–359. See especially A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *J. Org. Chem.*, **22**, 642 (1957).

(21) E. I. Heiba and P. S. Landis, *J. Catal.*, **3**, 471 (1964).

(22) Part II: J. Shabtai, L. H. Klemm, and D. R. Taylor, *J. Org. Chem.*, **33**, 1489 (1968).

(23) Part III: J. Shabtai, L. H. Klemm, and D. R. Taylor, *ibid.*, **33**, 1494 (1968).

(24) R. C. Greenler, *J. Chem. Phys.*, **37**, 2094 (1962). We are investigating such possibilities at the present time.

(25) E. B. Barnett and F. G. Sanders, *J. Chem. Soc.*, 434 (1933).

(26) S. Dev, *J. Indian Chem. Soc.*, **25**, 315 (1948).

(27) (a) Our efforts to prepare this acid by Friedel-Crafts reaction of γ-valerolactone with toluene either according to the procedure of Phillips[24] or to that of Chaudhuri[24] gave a mixture of *meta* and *para* isomers as determined by pmr analysis. (b) Cyclization of the mixed saturated isomeric acids[28] gave both XXIX and 1-oxo-4,6-dimethyl-1,2,3,4-tetrahydronaphthalene, separable by vpc. The pmr spectrum of the latter ketone differs from that of XXIX principally in the aromatic region where it shows two overlapping signals at δ 6.8–7.2 for protons at C-5 and C-7 and a doublet (δ 7.82, J = 8 cps) for the proton at C-8.

(28) D. D. Phillips, *J. Amer. Chem. Soc.*, **77**, 3658 (1955).

(29) N. Chaudhuri, *Sci. Cult.* (Calcutta), **18**, 442 (1953).

TABLE II

COMPARATIVE PROPERTIES OF METHYL-SUBSTITUTED NAPHTHALENES ISOLATED FROM REACTION MIXTURES

Position(s) of methyl substituent(s)	Expt no.[a]	r_V[b]	Mp, °C		Picrate mp, °C		Styphnate mp, °C	
			Found	Lit.[c]	Found	Lit.[c]	Found	Lit.[c]
None[d]	14, 19	1.00	80–80.5	80.2	...	...	...	...
1[d]	8–19	1.77	Liquid	−30.8	...	...	...	...
2[d]	8–19	1.65	34–35	34.4	115–117	116–117	...	...
1,2[d]	6–10	3.08	Liquid	−1.6	130–132	131	142–143.5	143.5
1,2,3[e]	12, 13	4.74	27.5–28	27–28	142.5–143	142.5	...	...
1,2,4[d]	10, 16	4.52	54–55	54–55	147–148	148	123–124	123.5
1,2,7[d]	10, 16	3.85	Liquid	13[f]	129–131	129–131	158–159	159
1,2,3,4[e]	12, 14	8.89	107–107.5	107	182–183	182–183	...	...
1,2,4,7[d,g]	16	6.95	46–47	...	146–147	...	...	...
1,2,3,4,6[e]	13, 16	12.70	85–86	85	175–176	176	...	...
1,2,3,4,6,7[e]	12, 16	20.60	143–145	145	190–191	190.5	...	...

[a] Experiments from which methyl-substituted naphthalenes were isolated. [b] Retention volume, relative to naphthalene as internal standard, on a Bentone–Apiezon column (see text); helium flow rate, 85 cc/min; temperature, 170° for mono- and dimethylnaphthalenes and 200° for all others. [c] Unless otherwise indicated, data are from ref 31a. [d] Identified by direct comparison with an authentic sample. [e] Structure assigned on the basis of the physical properties given as well as of infrared and pmr spectra. [f] See ref 32. [g] See ref 30.

(see Experimental Section). The pmr and infrared spectra were in agreement with the assigned structure of 1,2,4,7-tetramethylnaphthalene (*vide infra*). The physical properties of our hydrocarbon, however, were different from those reported by Colonge and Grimaud for a product (derived from initial Friedel–Crafts alkylation of toluene by means of ethyl 2-methyl-2-penten-1-oate) to which they ascribe structure XXI without adequate proof.[30]

Experimental Section

Apparatus, Catalysts, and Procedure.—Reactions were carried out in a flow system consisting essentially of a vertically mounted 75 cm × 1.6 cm (i.d.) stainless steel tube, provided at the top with a constant-rate dropping funnel and connected at the outlet to a series of coolers and traps. The reactor tube was heated with a furnace (60 cm in length), equipped with three separately controlled heating coils, which by proper adjustment provided an isothermal zone 45 ± 3 cm in length. The temperature of this zone was measured to an estimated accuracy of ±3°.

In each run there was employed 80 g of fresh alumina catalyst in the form of a bed 40 cm long and situated in the isothermal zone. Catalyst A was prepared[9] by hydrolysis of freshly distilled aluminum isopropoxide with excess distilled water at 85–95°. The precipitate was washed thoroughly with distilled water, filtered, dried at 120° for 36 hr, powdered, and compressed in the form of 1/8-in. pellets. Catalyst B (Harshaw Chemical Co., Cleveland, Ohio, Grade AL-0104 alumina, 1/8-in. pellets) and catalyst C (Houdry Process Corp., Philadelphia, Pa., hard alumina, Grade HA-100, cylindrically extruded 1/8-in. pellets) were obtained commercially.

The catalyst bed was activated *in situ* before each experiment by heating at 650° for 16 hr in a stream of dry nitrogen. The desired reaction temperature was then established and absolute methanol (60–70 ml) was passed over the catalyst for 30–35 min. This was followed by the dropwise addition of a mixture of the reactants, *viz.* 1-naphthol (14.4 g, 0.1 mol) and absolute methanol (32 g, 1 mol), over a period of 2 hr. Finally, an additional portion of methanol (10 ml) was passed through the reactor. A constant flow of nitrogen (22 cc/min) was maintained throughout the experiment. In most cases liquid product started to appear in the first, water-cooled trap only after the lapse of 20–25 min. At the end of the reaction the catalyst was washed with benzene (50 ml) to elute remaining methylnaphthalenes, and was then removed from the tube and treated with boiling acetone to complete extraction of the more strongly adsorbed naphthols. Combined condensates and extracts were evaporated to remove solvents. The organic product was separated from a water layer, dissolved in ether, and washed with 10% aqueous sodium hydroxide and then with water. The alkaline extract was acidified with hydrochloric acid and extracted with ether. Evaporation of the ether solutions gave a neutral fraction and an acidic one.

For the neutral products from expt 1–9 separation of components was effected on an 8 ft × 3/8-in. (o.d.) column packed with 60–80 mesh acid-washed Chromosorb P impregnated with 10% Bentone-34 and 5% Apiezon L. The carrier gas was helium. The column temperature was 170° for oxohydronaphthalenes, naphthalene, and mono-, di-, and trimethylnaphthalenes and 200° for polymethylnaphthalenes. For acidic products separation was conducted through the combined use of two columns, one (6 ft × 0.25-in.) packed with 10% Apiezon L on Chromosorb P and the other (5 ft × 3/8-in.) packed with 10% Carbowax 20M on the same support. In expt 10–19 the neutral fraction was first distilled at 0.5 mm. The distillate (bp ≤160°) was then examined by vpc as before. The same columns were used for quantitative analysis of the reaction mixtures.

The distillation residues from runs 14–19 were subjected to liquid–solid chromatography on a column (40 cm × 3.2 cm) of Alcoa F-20 alumina by means of cyclohexane and then benzene–cyclohexane (1:1 v/v) as eluents. Total weights of eluted products were determined (see footnote *i*, Table I), but these compounds were not analyzed further. A yellow zone with a strong greenish fluorescence was separated from the column and extracted with hot chloroform. Evaporation of the extract and recrystallization of the residue from ethanol–chloroform gave perylene, yield determined by direct weight.

Data on the analytical results for the various runs are presented in Table I. The estimated absolute error in vpc percentages, as based on repeated analyses of the same product mixture and of synthetic mixtures, is ±0–0.7% for each component. The reproducibility of results, as determined by repeating experiments under identical reaction conditions, is ±0–1.5% (absolute) for each component.

Identification of Individual Components.—Hydrocarbons XI–XIV, XVII, XVIII, XXI, and perylene (mp 272–274°, lit.[31b] 273–274°) were identified by direct comparison (in various combinations of melting point, mixture melting point, relative retention volume (r_V) in vpc, infrared, and pmr spectra) with authentic reference samples and their derivatives (*cf.* Tables II and III). It might be noted that 1,2,4- and 1,2,7-trimethylnaphthalenes (XVII and XVIII) show three different signals of equal areas for methyl protons in their pmr spectra. The reference compounds in these cases were synthesized from purified samples of 1,4- and 2,7-dimethylnaphthalenes, respectively, by successive steps of chloromethylation and reduction.[32] If the third methyl group actually occupied any ring position other than C-2 or C-1, respectively, only two different methyl proton

(30) J. Colonge and E. Grimaud [*Compt. Rend.*, **231**, 580 (1950); *Bull. Soc. Chim. Fr.*, 857 (1951)] synthesized a hydrocarbon of mp −3° (picrate mp 151°, styphnate mp 118°), to which they assigned the structure of 1,2,4,7-tetramethylnaphthalene. This assignment was based on the unproved assumption that Friedel–Crafts alkylation of toluene by means of ethyl 2-methyl-4-penten-1-oate gives ethyl 2-methyl-4-(4-tolyl)pentanoate. It seems likely that these authors synthesized, instead, either an isomeric tetramethylnaphthalene or a mixture of isomers (*cf.* ref 27a).

(31) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IIIB, Elsevier Publishing Co., Amsterdam, 1956, (a) pp 1286–1288, (b) p 1505.

(32) W. Ried and H. Bodem, *Chem. Ber.*, **91**, 1354 (1958).

TABLE III

PROTON MAGNETIC RESONANCE CHARACTERISTICS OF SOME METHYL-SUBSTITUTED NAPHTHALENES[a]

Positions of methyl groups	Methyl protons: δ, ppm;[b] relative areas	Aromatic protons: δ, ppm (multiplicity); J, cps, assignment; relative areas
1,2 (XIV)	2.33, 2.41;[c] 0.9:1	6.9–8.0 m
1,2,3 (XVI)	2.31, 2.39, 2.54; *ca.* 1:1:1	7.2–8.0 m
1,2,4 (XVII)	2.31, 2.41, 2.51; *ca.* 1:1:1	6.94 s, H-3; 7.1–7.6 m, β protons at C-6 and C-7; 7.6–8.0 m, α protons at C-5 and C-8; *ca.* 1:2:2
1,2,7 (XVIII)	2.25, 2.32, 2.38; *ca.* 1:1:1	6.8–7.7 m
1,2,3,4 (XIX)	2.31; 2.51; 1:1	Symmetric A_2B_2 system centered at 7.59; 7.1–7.5 m, β protons at C-6 and C-7; 7.7–8.1 m, α protons at C-5 and C-8; 1:1
1,2,4,7 (XXI)[d]	2.20, 2.30, 2.41; 1:1:2	6.79 s, H-3; 7.01 (doublet of doublets) J = 8.5 and J = 1.5, H-6; 7.4–7.7 m,[e] H-5 and H-8; 1:1:1.9
1,2,3,4,6 (XXII)	2.31, 2.48, 2.50; *ca.* 2:1:2[f]	7.10 (doublet of doublets) J = 8.8 and J = 2.0, H-7; 7.5–7.9 m,[g] H-5 and H-8; 1:2
1,2,3,4,6,7 (XXIII)	2.36, 2.42, 2.55; *ca.* 1:1:1	7.65 s, α protons at C-5 and C-8

[a] Solvent, CCl_4. Relative areas of methyl aromatic protons are in good agreement with assigned structures. [b] All appear to be singlets, but overlapping is extensive in some cases. [c] I. C. Lewis [*J. Phys. Chem.*, **70**, 1667 (1966)] reports methyl proton signals at 2.47 and 2.57 for this compound in the same solvent. [d] Marked changes occur in this spectrum (others not investigated) on changing the solvent to $CDCl_3$; observed data, δ 2.37, 2.49, 2.54—areas 1 : 2 : 1; plus entire aromatic region shifted downfield by *ca.* 20 cps. The change in relative areas of the three methyl proton signals is consistent with the presence in the molecule of four magnetically distinguishable methyl groups. [e] This region consists of a doublet at δ 7.60 ($J \simeq 8$ cps) for the proton at C-5 and a superimposed singlet at δ 7.57 for that at C-8. [f] The ratio of areas for the signals at 2.48 and 2.50 is based on visual observation of the spectrum. [g] This region consists of a doublet at δ 7.77 ($J \simeq 9$ cps) for the proton at C-8 and an adjacent broadened singlet at δ *ca.* 7.63 for that at C-5.

signals should be observed.[33] 2,7-Dimethylnaphthalene (XV) was not isolated but was identified only by r_V (direct comparison with authentic samples of all possible dimethylnaphthalenes).

1,2,3-Tri- (XVI), 1,2,3,4-tetra- (XIX), 1,2,3,4,6-penta- (XXII), and 1,2,3,4,6,7-hexamethylnaphthalenes (XXIII) were identified by pmr and infrared spectra and by comparison of melting points of the hydrocarbons and their picrates with literature values. The pmr spectrum of XIX clearly shows an A_2B_2 pattern for protons in the unsubstituted ring and two singlets (of equal areas) for two sets of equivalent methyl groups. The infrared spectrum in the 1650–2000-cm^{-1} region (measured in CS_2) shows a typical pattern for an *ortho*-disubstituted benzene ring,[34] *i.e.*, singlets at 1693 and 1740 cm^{-1}, a doublet at 1793 and 1818 cm^{-1}, and a triplet at 1887, 1912, and 1939 cm^{-1}. The infrared spectrum of XVI shows the same pattern (1686, 1743, 1786, 1811, 1890, 1910, and 1937 cm^{-1}) plus one other band (1713 cm^{-1}), possibly owing to the lone hydrogen in the methyl-substituted ring. XXII shows (intensities: s = strong, m = medium, w = weak) $\nu_{max}^{CS_2}$ 769 m cm^{-1}, 810 s, 872 s, 1045 m, 1187 m, 2930 s; $\nu_{max}^{CHCl_3}$ 1384 s cm^{-1}, 1452 s, 1517 s, 1595 m, 1629 m, 1721 w, 1760 w, 1907 w. XXIII has $\nu_{max}^{CS_2}$ 865 s cm^{-1}, 1003 m, 2930 s, 2950 s; $\nu_{max}^{CHCl_3}$ 1378 s cm^{-1}, 1447 s, 1502 m, 1590 m, 1705 m, 1772 w.

The pmr spectrum of XXII shows features characteristic of the presence of two aromatic protons in a vicinal α,β arrangement on the ring and of one other aromatic proton in an α position. Only three isomeric structures, 1,2,3,4,6-, 1,2,3,5,6-, and 2,3,4,-5,6-pentamethylnaphthalenes, are consistent with this spectral evidence. The presence of strong CH out-of-plane deformation bands at 810 (for two adjacent free hydrogen atoms) and 872 cm^{-1} (lone aromatic hydrogen)[35] in the infrared spectrum corroborates these possible assignments. A final choice was made on the basis of the pattern of absorption bands (1721, 1760, and 1907 cm^{-1}) in the 1650–2000-cm^{-1} region which is consistent with the presence of all of the aromatic hydrogen atoms in one ring (1,2,4-trisubstituted benzene) as occurs in the 1,2,3,4,6 isomer, but is inconsistent with the presence of two aromatic hydrogen atoms in one ring and one in the other (*i.e.*, for superposition of bands from a pentasubstituted benzene and a 1,2,3,4-tetrasubstituted benzene) as occur in the other two possible isomers. The pmr spectrum of XXIII shows features of three equally intense methyl proton signals and a singlet for two unoccupied α positions in the ring. Again three isomeric structures, 1,2,3,4,6,7-, 1,2,3,5,6,7-, and 2,3,4,5,6,7-hexamethylnaphthalenes, are consistent with this evidence. The infrared spectral pattern for XXIII (medium band at 1705 and a much weaker band at 1772 cm^{-1}) is typical of a 1,2,4,5-tetrasubstituted benzene ring (as occurs in the 1,2,3,4,6,7 isomer), but is inconsistent with the presence of a pentasubstituted ring (as occurs in each of the other possible isomers). Corroborating the assignment is also the presence of a single strong band (at 865 cm^{-1}) for a lone aromatic hydrogen. One might also note that bands at 870 and 881 cm^{-1} in the infrared spectrum of XXI are apparently due to the lone hydrogens at C-3 and C-8, while a strong band at 810 cm^{-1} can be assigned to the two adjacent hydrogens at C-5 and C-6.

The tentative assignment of the last two peaks in the chromatogram from expt 13 to hepta- and octamethylnaphthalenes is based on a comparison of retention volumes of compounds XII–XXIII on a silicone rubber column with their reported boiling points and extrapolation of the results to those of the two higher components. The unidentified components were found to have proper boiling ranges for the assigned structures, *i.e.*, 350 ± 10 and 365 ± 10° (760 mm), respectively.

1-Methoxynaphthalene was isolated from expt 4: r_V = 5.1 at 170° (see Table III, footnote *b*); pmr spectrum: singlet, 3 H (δ 3.86) methoxy group; multiplet, 7 H (6.5–8.3) aromatic protons; identical in infrared spectrum and r_V with an authentic sample. 1-Methoxy-2-methylnaphthalene was isolated from expt 4: pmr spectrum: singlet, 3 H (δ 2.40) aromatic methyl group; singlet, 3 H (3.84) methoxy group; multiplet, 6 H (7.0–8.2) aromatic protons; ν_{max}^{neat} 1247 (Ar–O stretch) and 1092 cm^{-1} (Me–O).[36] Some of this ether was refluxed with pyridine hydrochloride[37] to give 2-methyl-1-naphthol. 2-Methyl-1-naphthol was isolated from expt 5: mp 63.5–64° (lit.[38] 63–64°); $\nu_{max}^{CS_2}$ 3620 cm^{-1} (OH); pmr spectrum (in CS_2): singlet (δ 2.17) methyl group, singlet (5.02) OH, and multiplet (6.9–8.1) aromatic protons; identical with a synthetic sample. 4-Methyl-1-naphthol was isolated from expt 3 and 5: mp 83–85° (lit.[37] 85°); pmr spectrum (in $CDCl_3$): slightly split singlet, 3 H (δ 2.56, J = 1 cps) methyl group; singlet, 1 H (5.42) OH; AB quartet centered at δ 6.84, 2 H ($\Delta\delta_{AB}$ = 26 cps, J_{AB} = 7.5 cps)[39] but with apparent long-range splitting ($J \simeq 1$ cps) in the downfield half—probably protons at C-2 and C-3; multiplet, 2 H (7.3–7.7) probably protons at C-6 and C-7; multiplet, 2 H (7.7–8.4) probably protons at C-5 and C-8; identical with a synthetic sample. 2,4-Dimethyl-1-naphthol was isolated from expt 3 and 5: mp 81–83° (lit.[37] 82–83°); pmr spectrum: two singlets, 3 H each (δ 2.22, 2.51) methyl groups; singlet, 1 H (4.80) OH; singlet, 1 H (6.93) proton at C-3; multiplet, 4 H

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(7.2–8.2) aromatic protons at C-5 to C-8; identical with a synthetic sample.

1-Oxo-2,2-dimethyl-1,2-dihydronaphthalene (IX) was isolated from expt 6: pmr spectrum: singlet, 6 H (δ 1.24) methyl groups; AB quartet centered at δ 6.25, 2 H ($\Delta\delta_{AB}$ = 17 cps, J = 9.5 cps)[39] protons at C-3 and C-4; multiplet, 3 H (7.0–7.7) protons at C-5, C-6, and C-7; multiplet, 1 H (7.8–8.2) proton at C-8; ν_{max}^{neat} 690 m cm^{-1}, 790 s, 890 m, 994 m, 1305 m, 1468 m, 1600 m, 1684 s, 2880 m; r_V = 2.4 at 170°; identical with a synthetic sample. It might be noted that the CH out-of-plane deformation frequency (at 790 cm^{-1}) for the four adjacent aromatic hydrogens is considerably higher than that of *o*-xylene (742)[40a] or of 1,2,3,4-tetrahydronaphthalene (742).[40b] This may result from the combined conjugation effects of the carbonyl group and the double bond in IX. A weaker shift in the same direction was found for *o*-methylstyrene (772).[41]

1-Oxo-4,4-dimethyl-1,4-dihydronaphthalene (X) was isolated from expt 3 and 6: mp 70–71° (lit.[42] 69.5–70.5°); pmr spectrum: singlet, 6 H (δ 1.43) methyl groups; AB quartet centered at δ 6.55, 2 H ($\Delta\delta_{AB}$ = 33 cps, J_{AB} = 10 cps)[39] protons at C-2 and C-3; multiplet, 3 H (7.0–7.6) protons at C-5 to C-7; multiplet, 1 H (7.8–8.2) proton at C-8; $\nu_{max}^{CS_2}$ 770 s, cm^{-1}, 843 s, 1039 m, 1093 m, 1158 s, 1309 s, 1379 m, 1401 m, 1471 s, 1484 m, 1604 s, 1665 s, 2985 s, 3033 m; r_V = 4.1 at 170°; identical with a synthetic sample. The CH out-of-plane deformation frequency (at 770 cm^{-1}) for four adjacent hydrogens falls between that of IX and that of *o*-xylene.

Analytical Methods.—Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Pmr spectra were obtained by means of a Varian Associates A-60 spectrometer. Tetramethylsilane was used as an internal reference and, unless otherwise noted, carbon tetrachloride was used as a solvent. Infrared spectra were obtained by means of a Beckman IR-7 spectrophotometer. Solutions in CS_2 or $CHCl_3$ (6–10% by wt) were examined in a cell of 0.1-mm thickness and pure liquids were examined directly between NaCl plates.

Source and Synthesis of Reference Compounds. A. Oxygen-Containing Compounds.—2-Methyl-1-naphthol[43,44] and 1-oxo-4,4-dimethyl-1,4-dihydronaphthalene[42] were prepared by reported procedures. 1-Methoxynaphthalene (Distillation Products) was purified by distillation *in vacuo*. It was converted into 4-methoxy-1-naphthaldehyde[37] [pmr spectrum: singlet (δ 3.67) methoxy group; AB quartet centered at δ *ca.* 6.85 ($\Delta\delta_{AB} \simeq$ 64 cps, J_{AB} = 7.5 cps)[39] probably protons at C-2 and C-3, but with the downfield half overlapping a multiplet (7.1–7.7), probably protons at C-6 and C-7; multiplets (7.8–8.2 and 9.1–9.4) probably protons at C-5 and C-8; singlet (9.97) aldehyde group] which was reduced to 1-methoxy-4-methyl-naphthalene[37] [pmr spectrum: slightly split singlet, 3 H (δ 2.46, J = 0.8 cps) aromatic methyl group; singlet 3 H (3.64) methoxy group; AB quartet centered at δ 6.65, 2 H ($\Delta\delta_{AB}$ = 35 cps, J_{AB} = 7.5 cps)[39] but with apparent long-range splitting (J = 0.8 cps) in the downfield half—probably protons at C-2 and C-3; multiplet, 2 H (7.1–7.5) probably protons at C-6 and C-7; multiplet with secondary splitting (J = 0.8 cps) 1 H (7.5–7.9) and multiplet 1 H (8.1–8.5) probably protons at C-5 and C-8]. Demethylation of this ether[37] gave 4-methyl-1-naphthol (VI).

To a stirred, ice-cold solution of 109.5 g (0.64 mol) of 1-methoxy-4-methylnaphthalene in 350 ml of methylene chloride was added 261 g of anhydrous stannic chloride and then (dropwise) 110 g (0.7 mol) of dichloromethyl *n*-butyl ether.[45] The stirred solution was allowed to attain room temperature and then was poured onto ice. The organic phase (plus extracts of the aqueous phase with the same solvent) was washed successively with 5% aqueous sodium bicarbonate solution and water, dried, and evaporated: yield 112 g (88%) of 1-methoxy-4-methyl-2-naphthaldehyde; mp 88–90° (after crystallization from ethanol); pmr spectrum, singlet, 3 H (δ 2.60) methyl group; singlet, 3 H (4.05) methoxy group; multiplet, 5 H (7.3–8.3) aromatic protons; singlet, 1 H (10.42) aldehyde group; lit.[37] mp 90°.

According to published directions[37] the immediately foregoing aldehyde was converted first into 1-methoxy-2,4-dimethylnaphthalene [pmr spectrum: singlet (δ 2.25) probably methyl at C-2; slightly split singlet (2.41, $J \simeq$ 1 cps) probably methyl at C-4; singlet (3.66) methoxy group; singlet (6.82) proton at C-3; multiplet (7.0–8.3) aromatic protons in unsubstituted ring] and then into 2,4-dimethyl-1-naphthol.

1-Oxo-2,2-dimethyl-1,2,3,4-tetrahydronaphthalene.—To a cold (10–15°), stirred mixture of 24.6 g (0.17 mol) of 1-tetralone (Aldrich Chemical Co.), 59.5 g (0.42 mol) of methyl iodide, and 100 ml of benzene in an atmosphere of nitrogen was added in portions over a period of 30 min a mineral oil dispersion of sodium hydride (6.7 g, 0.28 mol). The mixture was stirred at 55–60° for 5 hr, refluxed for 1 hr, stirred at room temperature overnight, and then poured into excess methanol. The residue from evaporation of solvents was extracted with ether. The ether extract was washed successively with water, 10% aqueous sodium carbonate solution, and water and then distilled: yield 21 g (71%); bp 88–89° (1 mm); n^{24}D 1.5395 [lit.[46] bp 124–126° (11 mm); n^{25}D 1.5388]; $\nu_{max}^{CCl_4}$ at 1690 cm^{-1} (strong, C=O); pmr spectrum: singlet, 6 H (δ 1.12), methyl group; two triplets, 4 H (1.84 and 2.87, J = 6 cps) dimethylene group; multiplet, 3 H (6.9–7.5) aromatic protons at C-5, C-6, and C-7; multiplet, 1 H (7.8–8.2) proton at C-8. These spectra were identical with those of an authentic sample made by a different method.[46]

1-Oxo-2,2-dimethyl-1,2-dihydronaphthalene (IX).—A mixture of 15.1 g (0.087 mol) of the preceding ketone, 19.6 g (0.11 mol) of N-bromosuccinimide, 58 ml of carbon tetrachloride, and 0.2 g of benzoyl peroxide was refluxed in an atmosphere of nitrogen for 5 hr. The cooled mixture was filtered to remove precipitated succinimide and evaporated to remove solvent. The residue was refluxed with 150 ml of 10% ethanolic potassium hydroxide for 45 min and the solvent was again evaporated. This residue was treated with water and extracted with ether. Distillation gave 9.8 g (65%) of IX, bp 72–74° (0.4 mm), n^{25}D 1.5725 (lit.[46] n^{24}D 1.5705).

B. Hydrocarbons.—Perylene was commercially available (Aldrich Chemical Co.). Purified samples of naphthalene, all mono- and dimethylnaphthalenes, and four trimethylnaphthalenes, were available from previous studies.[47] Reported procedures were followed for the syntheses of 1,2,4- and 1,2,7-trimethylnaphthalenes.[32] 1,2,4,7-Tetramethylnaphthalene was synthesized by the following series of steps.

4-(4-Tolyl)-3-penten-1-oic Acid (XXVII).—β-(4-Methylbenzoyl)-propionic acid[25,26] [pmr spectrum, singlet (δ 2.39) methyl group, symmetric A_2B_2 multiplet centered at δ 3.02 ($\Delta\delta_{AB}$ = 29 cps, $J_{AB}/\Delta\delta_{AB} \simeq$ 0.2)[48] dimethylene group, a slightly altered AB quartet centered at δ 7.58 ($\Delta\delta_{AB}$ = 38 cps, J_{AB} = 8 cps)[39] aromatic protons, singlet (11.06) carboxylic acid] was converted into ethyl β-(4-methylbenzoyl)propionate, mp 42–44° (lit. 42–43.5°), by a reported procedure:[26] $\nu_{max}^{CCl_4}$ 1735 (ester) and 1795 cm^{-1} (ketonic C=O); pmr spectrum, triplet (δ 1.19, J = 7 cps) methyl moiety of ester group, singlet (2.32) aromatic methyl group, symmetric A_2B_2 multiplet centered at δ 2.87 ($\Delta\delta_{AB}$ = 31 cps, $J_{AB}/\Delta\delta_{AB} \simeq$ 0.2)[48] dimethylene group, quartet (δ 4.07, J = 7 cps) methylene moiety of ester group, and an AB quartet centered at δ 7.49 ($\Delta\delta_{AB}$ = 38 cps, J_{AB} = 8 cps)[39] aromatic protons.

To a rapidly stirred cold (0°) solution of 30 g of this ester in a mixture of 100 ml of dry benzene and 100 ml of anhydrous ether was added dropwise a 1 molar equiv of methylmagnesium iodide in ether. After removal of most of the ether by distillation, the remaining mixture was refluxed for 1 hr by itself and then further with added dilute sulfuric acid. Extraction of the organic layer with excess aqueous sodium hydroxide and acidification of the aqueous extract yielded 17.6 g (63%) of crude unsaturated acids, presumably a mixture of 4-(4-tolyl)-4-penten-1-oic acid (XXVI) and XXVII: $\nu_{max}^{CS_2}$ 810, 828 (2 vicinal aromatic H, trisubstituted ethylene), 901 (C=CH$_2$), and 1720 cm^{-1} (C=O). The pmr spectrum (*vide infra*) indicated the presence of *ca.* 25–30% XXVI and 70–75% XXVII therein.

A sample of the mixed unsaturated acids in absolute ethanol was hydrogenated at 1 atm pressure by use of prereduced Adams platinum catalyst until the original faster rate of reaction due to the presence of XXVI[49] had terminated. The partially saturated mixture of acids was crystallized from carbon tetrachloride

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to give prisms of XXVII: mp 83–85°; $\nu_{max}^{CS_2}$ 808 and 1715 cm^{-1}; pmr spectrum: singlet, 3 H (δ 1.95) vinylic methyl group; singlet, 3 H (2.25) aromatic methyl group; doublet, 2 H (3.16, J = 7 cps) methylene group; triplet, 1 H (5.85, J = 7 cps) vinylic proton; distorted AB spectrum, 4 H (6.8–7.4) aromatic protons; singlet, 1 H (12.25) carboxylic acid group. Small splittings (*ca.* 1 cps) were observable in all pmr signals except that at δ 2.25 and possibly those in the aromatic region.

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.96; H, 7.49.

By difference, the pmr spectrum of XXVI (as ascertained from the mixed acids) is found to be a singlet (δ 2.25) aromatic methyl group which presumably overlaps the upfield half of an A_2B_2 multiplet centered at *ca.* δ 2.4 for the dimethylene group, doublet (5.10, J = 15 cps) vinylic methylene group, multiplet (6.8–7.4) aromatic protons, and singlet (12.4) carboxylic acid group.

1-Oxo-2,2,4,7-tetramethyl-1,2,3,4-tetrahydronaphthalene (XXX).—Hydrogenation of 14 g of preceding mixed unsaturated acids until nearly an equimolar quantity of hydrogen had been absorbed gave 13 g (92%) of γ-(4-tolyl)valeric acid[27a] (XXVIII): $\nu_{max}^{CS_2}$ 807 (two vicinal aromatic H) and 1710 cm^{-1} (C=O); pmr spectrum, doublet (δ 1.22, J = 7 cps) aliphatic methyl group, singlet (2.25) aromatic methyl group superimposed on multiplet (1.5–2.9) for other aliphatic protons, singlet (6.97) aromatic protons, singlet (11.74) carboxylic acid group. This saturated acid was cyclized to 1-oxo-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene (XXIX) by the method of Phillips:[28] $\nu_{max}^{CS_2}$ 815 and 825 (aromatic C–H) and 1690 cm^{-1} (C=O); pmr spectrum: doublet, 3 H (δ 1.30, J = 7 cps) methyl group at C-4; singlet (2.26) methyl group at C-7, superimposed on complex absorption at δ 1.5–3.2—total 8–9 H; singlet, 2 H (7.09) protons at C-5 and C-6; singlet (7.64) proton at C-8.[27b]

To a cold (10°), stirred mixture of 8.5 g (0.049 mol) of ketone XXIX, 7.5 ml (0.12 mol) of methyl iodide, and 29 ml of benzene in an atmosphere of nitrogen was added a mineral oil dispersion of sodium hydride (7.2 g, 0.3 mol). The mixture was stirred and refluxed for 7 hr, whereupon the theoretical amount of hydrogen had been evolved. The reaction mixture was poured into excess methanol. The residue from evaporation of the solvents was extracted with ether. The dried ether solution was distilled to give 8 g (81%) of XXX: bp 86–89° (0.15 mm); $\nu_{max}^{CS_2}$ 820 (aromatic C–H) and 1685 cm^{-1} (C=O); pmr spectrum: two singlets, *ca.* 6 H (δ 1.08, 1.16) *gem*-methyl groups at C-2; doublet, *ca.* 3 H (1.29, J = 7 cps) methyl group at C-4; singlet, *ca.* 3 H (2.26) methyl group at C-7, superimposed on complex multiplet *ca.* 3 H (1.5–3.3) for ring protons at C-3 and C-4; pseudo-doublet, 2 H (7.13, 7.16) protons at C-5 and C-6; singlet, 1 H (7.72) proton at C-8.

An analytical sample was obtained as a light yellow liquid, bp 88–89° (0.1 mm), n^{23}D 1.5250.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.21; H, 9.08.

1-Hydroxy-2,2,4,7-tetramethyl-1,2,3,4-tetrahydronaphthalene (XXXI).—To a stirred solution of 1 g of sodium borohydride in 20 ml of absolute ethanol was added, dropwise, 6 g of ketone XXX. Stirring was continued for 2 hr, and then the mixture was poured into 55 ml of 9% aqueous acetic acid. An ether extract of the mixture was washed with aqueous sodium bicarbonate and then with water, dried, and evaporated to give a liquid which rapidly solidified. Crystallization from pentane gave 4.5 g (74%) of prisms: mp 81.5–83.5° (raised to 85–86° on further recrystallization); $\nu_{max}^{CCl_4}$ 820 (aromatic C–H), 3620 and 3650 (OH); pmr spectrum: two singlets, 6 H (δ 0.74, 1.04), *gem*-methyl groups at C-2; doublet (1.20, J = 7 cps) methyl group at C-4, singlet (2.23) methyl group at C-7—which overlap complex absorptions in the region of δ 1.1–3.2; doublet (4.19, J = 8 cps) OH; multiplet, 2 H (6.7–7.2) and broad singlet, 1 H (7.31) aromatic protons.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.17; H, 9.80.

1,2,4,7-Tetramethylnaphthalene (XXI).—A powdered mixture of 1.7 g of the preceding carbinol and 2 g of freshly fused potassium bisulfate was heated in a distillation apparatus at reduced pressure to give 1.1 g of distillate, bp 122–124°, shown to be a mixture of products (probably tri- and tetramethyldihydronaphthalenes) by means of vpc, infrared, and pmr analyses. A mixture of this distillate, 1.43 g of 2,3-dichloro-5,6-dicyanoquinone (DDQ), and 20 ml of benzene was refluxed for 1 hr, cooled, treated with 20 ml of petroleum ether (bp 30–60°), and filtered to remove the reduced quinone. The filtrate was chromatographed by means of 15 g of Woelm neutral alumina and benzene–petroleum ether (1:1 v/v) as eluent. Vpc analysis of the 610 mg of liquid which remained on evaporation of the effluent showed the presence of 74% of XXI, 11% of mixed trimethylnaphthalenes, and unidentified components therein. Preparative vpc gave XXI as prisms: mp 46–47°; $\nu_{max}^{CS_2}$ 810 s cm^{-1}, 870 s, 881 m, 1015 m, 1035 m, 1172 m, 2930 s, 2950 s, 2980 m, 3020 m; $\nu_{max}^{CHCl_3}$ 1382 s, 1440 s, 1515 s, 1606 s, 1623 s.

Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.19; H, 8.87.

The picrate formed bright orange needles from absolute ethanol, mp 146–147°.

Anal. Calcd for $C_{20}H_{19}N_3O_7$: C, 58.11; H, 4.63; N, 10.17. Found: C, 57.93; H, 4.76; N, 10.66.

Registry No.—I, 90-15-3; IX, 16020-15-8; X, 16020-16-9; XXI, 16020-17-0; XXI picrate, 16020-18-1; XXVII, 16020-19-2; XXX, 16020-20-5; XXXI, 16020-21-6; methanol, 67-56-1; 1-methoxy-4-methyl-2-naphthaldehyde, 16020-22-7; 1-oxo-2,2-dimethyl-1,2,-3,4-tetrahydronaphthalene, 2,977-45-9.

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Alumina-Catalyzed Reactions of Hydroxyarenes and Hydroaromatic Ketones. II. Reactions of 1-Oxo-2,2-dimethyl-1,2-dihydronaphthalene, 1-Oxo-4,4-dimethyl-1,4-dihydronaphthalene, and 1-Methoxynaphthalene with Methanol[1a]

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The alumina-catalyzed reactions of 1-oxo-2,2-dimethyl-1,2-dihydronaphthalene (IX), 1-oxo-4,4-dimethyl-1,4-dihydronaphthalene (X), and 1-methoxynaphthalene (III) were studied at 320–420° in the presence of excess methanol. At 350° IX undergoes smooth reduction–rearrangement to form 1,2-dimethylnaphthalene in 84–98% yield (based on IX converted) in a reaction which has a low requirement for catalyst acidity. The reactions of X are distinctly dependent on catalyst acidity; 1,2,3,4-tetramethylnaphthalene and 1,2,3,4,6-pentamethylnaphthalene are main products (78–85 mol %) in the presence of strongly acidic alumina, whereas 1,1,3-trimethyl-1,2-dihydronaphthalene is formed as main product (>70% yield based on X converted) over weakly acidic catalysts. At 280–350° III yields oxygen-containing compounds (1-naphthol, methylated 1-naphthols, IX, and X) and methylnaphthalenes of the same array as obtained from 1-naphthol (I). Over weakly acidic catalysts at 280–350° the conversion of III is considerably lower than that of I, but this difference decreases with increasing catalyst acidity. At 420° over strongly acidic alumina the product distributions from III and I are nearly identical. Mechanistic aspects of the reactions are discussed.

In the preceding paper[2] it was shown that 1-naphthol (I) reacts with methanol at 350–550° in the presence of alumina catalysts to form relatively simple mixtures of methylnaphthalenes. At 275–300°, on the other hand, the reaction product contains 35–60% of oxygen-containing compounds, which include 2-methyl- and 4-methyl-1-naphthols, 2,4-dimethyl-1-naphthol, 1-methoxynaphthalene (III), 1-oxo-2,2-dimethyl-1,2-dihydronaphthalene (IX), and 1-oxo-4,4-dimethyl-1,4-dihydronaphthalene (X).[3] The present study is concerned with alumina-catalyzed reactions of methanol with compounds III, IX, and X in an effort to clarify the roles of the latter as possible intermediates in the ring-methylation process and to develop methods of preparation for selected polymethylnaphthalenes. Catalysts employed in the study were A (pure alumina, obtained by hydrolysis of aluminum isopropoxide),[2] C (Houdry hard alumina),[2] and D (alumina derived from potassium aluminate).[4] The apparatus and procedure were similar to those employed previously.[2] Reactions were carried out in a nitrogen atmosphere at temperatures of 280–420°. A fresh portion of alumina catalyst was used for each experiment. The molar ratio of methanol to III, IX, or X was 52:1 in all runs. Individual compounds were isolated from the products by preparative gas chromatography and identified by a combination of infrared and pmr spectral methods as well as, in most cases, by conversion into derivatives or by comparison with reference samples synthesized by independent means. Quantitative analysis of reaction products was carried out by means of gas chromatography.

Reactions of 1-Oxo-2,2-dimethyl-1,2-dihydronaphthalene (IX).—As seen from Table I, essentially only one product, 1,2-dimethylnaphthalene (XIV), is obtained from reaction of IX at 350° over the weakly acidic[4] catalysts D and C (expt 1 and 2). At this temperature a higher over-all conversion of IX is obtained with the strongly acidic[4] catalyst A (expt 3), but the product contains, in addition to XIV, small amounts of 2-methylnaphthalene (XIII), 1,2,3-trimethylnaphthalene (XVI), and 1,2,4-trimethylnaphthalene (XVII). XIV remains the predominant product at 420° with either catalyst C or A (expt 4 and 5), but the yield of trimethylnaphthalenes is somewhat increased.

The formation of 1,2-dimethylnaphthalene from IX involves the processes of oxygen elimination and skeletal rearrangement. Conceivably either process might occur first, or the two could occur simultaneously. A particularly attractive mechanism is presented in Scheme I where ketone IX is depicted as undergoing initial reduction (by hydrogen transfer from a reducing agent such as methanol or formaldehyde)[2] to carbinol XXXII, which subsequently undergoes dehydration with attendant neopentyl-type rearrangement of a methyl group from C-2 to C-1. In Scheme I the dehydration–rearrangement is represented as a concerted process with aspects of γ participation[5] and of anchimeric assistance by the migrating methyl group. The formation of a carbonium ion intermediate, in a stepwise process wherein both the hydroxide ion and (subsequently) the proton are lost from C-1, is also possible (*cf.* studies on dehydration of neopentyl alcohol over alumina).[5] Although XXXII could not be detected in the reaction products, it was found that this carbinol (synthesized separately in 97% yield by borohydride reduction of IX) does, indeed, undergo facile, quantitative conversion into XIV under the conditions of expt 2. Allylic rearrangement of XIVa to XIV should occur readily by proton transfer on the catalyst surface.

Alternatively, rearrangement might precede reduction, as shown in Scheme II. The mechanism is analogous to that proposed by Marvell and Magoon[6] for the dienone–phenol rearrangement of IX in sulfuric

(1) (a) This investigation was supported by Research Grants No. CA-5969 from the National Cancer Institute and No. GM 12730 from the National Institute of General Medical Sciences, U. S. Public Health Service. (b) On leave from the Department of Chemistry, Weizmann Institute of Science, Rehovoth, Israel. (c) Research Assistant, 1964–1967.

(2) Part I: L. H. Klemm, J. Shabtai, and D. R. Taylor, *J. Org. Chem.*, **33**, 1480 (1968).

(3) For simplicity, compounds and catalysts are designated by the same Roman numerals and capital letters, respectively, as used in part I.[2]

(4) H. Pines and W. O. Haag, *J. Amer. Chem. Soc.*, **82**, 2471 (1960).

(5) H. Pines and J. Manassen, *Advan. Catal.*, **16**, 80 (1966); C. N. Pillai and H. Pines, *J. Amer. Chem. Soc.*, **83**, 3274 (1961).

(6) E. N. Marvell and E. Magoon, *ibid.*, **76**, 5118 (1954).

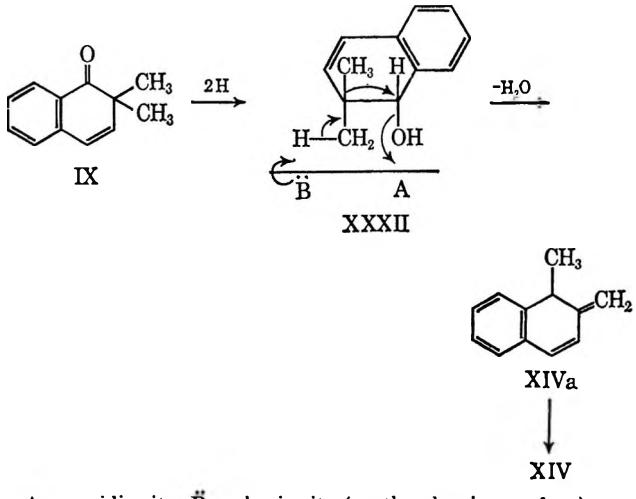
TABLE I

ALUMINA-CATALYZED REACTIONS OF 1-OXO-2,2-DIMETHYL-1,2-DIHYDRONAPHTHALENE (IX) IN THE PRESENCE OF METHANOL[a]

Expt no.	1	2	3	4	5
Catalyst	D	C	A	C	A
Reaction temp, °C	350	350	350	420	420
Conversion of IX, mol %	75	84	100	100	100
Product component,[b] mol %					
2-Methyl-N (XIII)	<0.1	0.1	4.6	4.5	4.0
1,2-Dimethyl-N (XIV)	74.5	83.5	84.0	74.0	76.0
1,2,3-Trimethyl-N (XVI)	<0.1	0.2	6.0	4.9	10.2
1,2,4-Trimethyl-N (XVII)	...	<0.1	1.7	1.3	2.8
Unidentified[c]	...	...	(2.8)	(5.3)	(5.8)

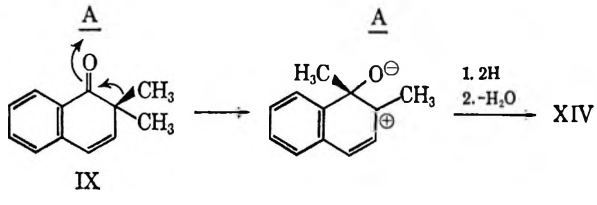
[a] Starting materials used in each experiment were 2 g (0.012 mol) of IX and 20 g (0.63 mol) of methanol. [b] Calculated on the basis of 100 mol of starting IX (including unreacted material). Differences between conversion and total product figures represent losses due to carbonaceous deposits on the catalyst. N = naphthalene. [c] Percentage by weight of total product. Includes unidentified chromatographic peaks and nondistillable residues.

SCHEME I



A = acidic site; B = basic site (on the alumina surface)

SCHEME II



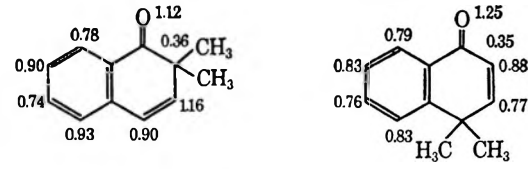
acid–acetic anhydride,[7] except that A is considered to be an acidic site on the alumina surface instead of a proton in solution. Also, the heterogeneous process leads to hydrocarbon XIV, while the homogeneous process gives, instead, 3,4-dimethyl-1-acetoxynaphthalene by reintroduction (from the solvent) of an oxygen function at a position *para* to the original OH.

1,2,3-Trimethylnaphthalene might result from initial direct electrophilic attack of a methyl group at C-3 of IX (see calculated superdelocalizability values in Scheme III[8]) followed by reduction–rearrangement of the hypothetical intermediate 1-oxo-2,2,3-trimethyl-1,2-dihydronaphthalene in the same manner as shown in Scheme I or Scheme II, or from initial rearrangement of IX to 2,3-dimethyl-1-naphthol (or its anion), methylation at C-2, and finally reduction–rearrangement as before. Several mechanistic pathways, each of low

(7) E. N. Marvell and A. O. Geiszler, *J. Amer. Chem. Soc.*, **74**, 1259 (1952).

SCHEME III

SUPERDELOCALIZABILITIES FOR ELECTROPHILIC ATTACK IN IX AND X(S_r, IN UNITS OF β_0^{-1})[a]



[a] See ref 8.

probability, could account for the small yields of 2-methylnaphthalene and of 1,2,4-trimethylnaphthalene.

Reactions of 1-Oxo-4,4-dimethyl-1,4-dihydronaphthalene (X).—As seen from Table II the main products formed by the reaction of compound X with methanol over catalyst A (expt 6–9) are 1,2,3,4-tetramethylnaphthalene (XIX) and 1,2,3,4,6-pentamethylnaphthalene (XXII). These components are free from isomers. At 320° XIX is the major product, but its relative yield decreases whereas that of XXII increases with increasing reaction temperature, up to 375°. At 420° a significant amount of 1,2,3,4,6,7-hexamethylnaphthalene (XXIII) and small amounts of hepta- and octamethylnaphthalenes (Table II, footnote *d*) are also formed. At 375° (expt 8) the reaction can be conveniently employed as a method for the preparation of XXII, since the latter is easily freed (by distillation) from the small amounts of lower methylnaphthalenes present.

At 320° with the weakly acidic catalysts C and D the reaction is strikingly different from that found with catalyst A. 1,1,3-Trimethyl-1,2-dihydronaphthalene (XXXIII) is the main product obtained, whereas XIX and XXII are formed in only low yields with catalyst C (expt 10) or in trace amounts with catalyst D (expt 11). At 420°, on the other hand, XXXIII is produced in low yields while XIX is the main component and smaller amounts of XXII (expt 12 and 13) are also formed. This gross change in product composition may be ascribed to marked increase in the acidities of catalysts C and D with increase of temperature.[2]

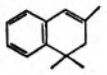
A plausible mechanistic pathway for conversion of X into XIX and XXII is presented in Scheme IV. First it is assumed that X is transformed to a common intermediate VIIc (or VIIb) by a mechanism analogous to that proposed by Arnold, *et al.*,[9] for the dienone–phenol rearrangement of X in sulfuric acid–acetic anhydride solution to give 3,4-dimethyl-1-acetoxynaphthalene. In the present case, however, A, an acidic site on the catalyst surface, assumes the role of a proton (*vide supra*) and the oxygen function is not acetylated. Indeed, in expt 10, conducted at 320° with the weakly acidic catalyst C (Table II, footnote *e*), a small amount of naphthol VIIb was isolated. In the presence of a more acidic catalyst, however, desorption of VIIb or its anion VIIc may not occur to any appreciable extent (*cf.* the strong adsorption of 1-naphthol on alumina).[2] Instead, this adsorbed substrate should be readily susceptible to further methylation at the 2 and 7 positions[2] to give higher homologs of IX. Such

(8) For method of calculation, see ref 2. The parameters used for IX and X were $h_O = 1.0$, $k_{C-O} = 1.0$; *cf.* A. Streitwieser, Jr., "Molecular Orbital Theory," John Wiley and Sons, Inc., New York, N. Y., 1961, p 123.

(9) R. T. Arnold, J. S. Buckley, and J. Richter, *J. Amer. Chem. Soc.*, **69**, 2322 (1947).

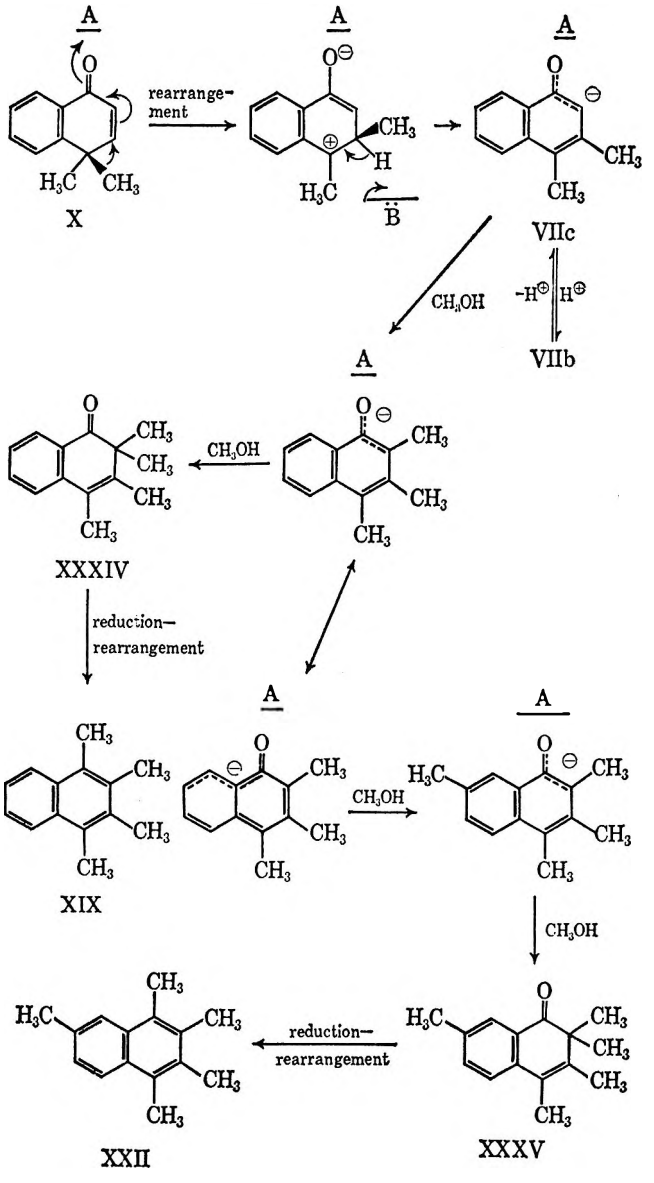
TABLE II

ALUMINA-CATALYZED REACTIONS OF 1-OXO-4,4-DIMETHYL-1,4-DIHYDRONAPHTHALENE (X) WITH METHANOL[a]

Expt. no.	6	7	8	9	10	11	12	13
Catalyst	A	A	A	A	C	D	C	D
Reaction temp, °C	320	350	375	420	320	320	420	420
Conversion of X, mol %	98	100	100	100	76	41	92	73
Product component,[b] mol %								
 (XXXIII)	3.7	2.0	1.3	Trace	54.5	37.2	4.5	5.2
1,2-Dimethyl-N (XIV)	...	1.0	2.9	0.5	...	...	...	...
1,2,3-Trimethyl-N (XVI)	2.4	2.8	3.4	0.8	Trace	...	3.5	3.4
1,2,4-Trimethyl-N (XVII)	0.7	0.9	0.6	0.8	...	...	...	...
1,2,3,4-Tetramethyl-N (XIX)	49.2	35.8	11.5	13.2	9.0	Trace	50.4	40.3
1,2,3,4,6-Pentamethyl-N (XXII)	34.5	45.2	71.6	64.4	4.6	...	26.1	18.9
1,2,3,4,6,7-Hexamethyl-N (XXIII)	...	...	Trace	13.0	...	...	...	...
Others[c]	(5.4)	(3.7)	(2.0)	(5.2)[d]	(9.7)[e]	(8.6)	(6.6)	(6.0)

[a] Total quantities of 2 g (0.012 mol) of X and 20 g (0.63 mol) of methanol were used as starting materials in each experiment. [b] See footnote *b*, Table I, but for starting X (rather than for IX). [c] Percentage by weight of total product. It includes unidentified chromatographic peaks and nondistillable residues. [d] Product contains 2.7 mol % of heptamethylnaphthalene and 1 mol % of octamethylnaphthalene, as based on gas chromatographic data only. [e] Of this total 23% is 3,4-dimethyl-1-naphthol (VIIb).

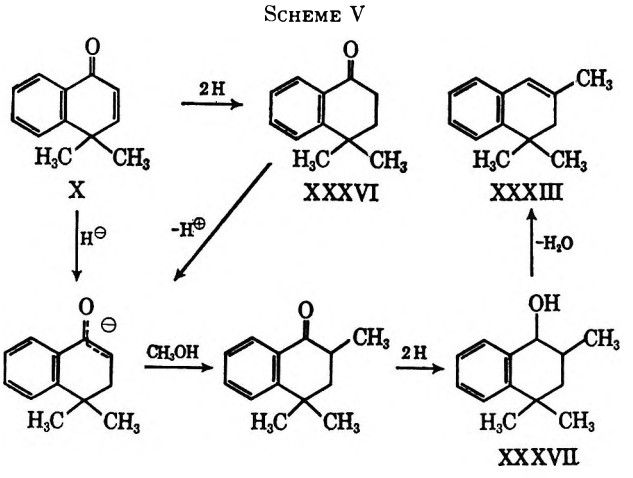
SCHEME IV



intermediate ketones (XXXIV and XXXV) were not isolated. However, they would be expected to undergo rapid reduction–rearrangement under the experimental conditions in analogy with IX (*vide supra*). The small amount of XVI may arise by methylation at C-2 followed by reduction–rearrangement (Scheme III).

In Scheme IV (and again in Scheme V) implications on the uncertain nature of the active methylating species have been avoided. The symbol CH_3OH is used merely to denote that methanol is the ultimate source of this electrophilic species.

SCHEME V



The operation of Scheme IV requires the presence of a catalyst of sufficiently high acidity in order to initiate the over-all process. At 320°, the very weakly acidic catalyst D would appear to be unable to effect molecular rearrangement of X, while the somewhat more acidic catalyst C can do so to a limited extent. Under the former conditions almost all of the X which reacts is converted into XXXIII, possibly *via* Scheme V. In analogy with the action of aluminohydrides in solution,[10] it is assumed that an alumina catalyst with sufficiently strong basic sites can initially furnish a hydride ion to the α,β-unsaturated ketone X (or, alternatively, abstraction of a proton may follow reduction of the C=C bond). Further methylation and reduction should give the intermediate carbinol XXXVII which could be dehydrated without skeletal rearrangement to XXXIII.[5] As a partial test of this mechanism the reaction of the saturated ketone

(10) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 2.

TABLE III

ALUMINA-CATALYZED REACTIONS OF 1-METHOXYNAPHTHALENE (III) AND 1-NAPHTHOL (I) WITH METHANOL[a]

Expt no.	14	15	16	17	18	19
Substrate	III	I	III	I	III	I
Catalyst	C	C	C	C	A	A
Reaction temp, °C	280	280	350	350	420	420
Conversion of III or I, mol %	32	55	56	78	98	100
Product component,[b] mol %						
1-Methoxy-N (III)	(68.0)[c]	4.8	(44.0)[c]	1.0	(1.6)[c]	...
1-Methoxy-2-methyl-N (IV)	0.1	0.3	...	Trace	...	...
1-Naphthol (I)	2.4	(45.0)[c]	1.3	(22.0)[c]	...	...
2-Methyl-1-naphthol (V)[d]	5.5	14.5	7.2	10.3	...	...
1-Oxo-2,2-dimethyl-1,2-dihydro-N (IX)	3.6	4.4	2.2	1.6	...	...
1- and 2-methyl-N (XII, XIII)	1.5	0.6	1.9	3.4	2.8	3.1
1,2-Dimethyl-N (XIV)	12.1	17.0	21.0	23.6	15.7	15.5
1,2,3-Trimethyl-N (XVI)	0.5	0.9	0.7	1.7	4.1	4.0
1,2,4-Trimethyl-N (XVII)	1.8	3.5	5.7	8.0	5.8	5.7
1,2,7-Trimethyl-N (XVIII)	1.2	2.0	4.3	6.4	21.5	18.0
1,2,4,7-Tetramethyl-N (XXI)	0.3	1.8	4.7	7.8	16.9	15.6
1,2,3,4,6-Pentamethyl-N (XXII)	...	0.7	1.8	4.5	15.6	18.7
Others[e]	1.0	2.5	4.1	6.0	11.4[f]	15.1[g]
Unidentified[h]	(1.5)	(1.7)	(1.0)	(3.5)	(3.0)	(3.5)

[a] Total quantities of 0.012 mol of III (or I) and 20 g (0.63 mol) of methanol were used as starting materials in each experiment. [b] See footnote *b*, Table I, but for starting III or I (rather than for IX). [c] Unreacted starting material. [d] Includes small amounts of 4-methyl-1-naphthol. [e] Includes 2,4-dimethyl-1-naphthol, 1-oxo-4,4-dimethyl-1,4-dihydronaphthalene, and other methylnaphthalenes. [f] Includes 3.3 mol % of 1,2,3,4,6,7-hexamethylnaphthalene (XXIII). [g] Includes 5.6 mol % of XXIII. [h] See footnote *c*, Table I.

XXXVI in the presence of methanol was studied under the conditions of expt 10. XXXVI gave a product which contained XXXIII as the main component (78% yield, based on XXXVI converted). The structure of XXXIII was established by spectral methods and by aromatization to 1,2,3-trimethylnaphthalene (93% yield) upon refluxing with a benzene solution of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). If the lone methyl group had been located at C-1 rather than at C-2 (in XXXVII) the aromatized product should have been 1,2,4-trimethylnaphthalene, instead.

It is apparent that X could serve as a convenient precursor for the synthesis of XXXIII on a preparative scale. Moreover, X should be useful as a substrate for evaluation of the relative acidities of alumina catalysts,[4] as adjudged by product compositions under the conditions of the experiments in Table II.

Reactions of 1-Methoxynaphthalene (III).—Table III summarizes the results of a comparative study of the reactions of methanol with III and with 1-naphthol (I). The higher conversion of I and some differences in the composition of products in expt 15, 17, and 19, as compared with previous results,[2] are due to the use of higher ratios of catalyst–naphthol and of methanol–naphthol in the present study. Under conditions of low acidity (catalyst C, 280–350°) III yields an array of oxygen-containing compounds, *e.g.*, I, V, and IX, and methylnaphthalenes closely similar to that obtained from I. However, the yields of individual components and the depth of methylation in the reactions with III are markedly lower than those with I (*cf.* expt 14–17). The formation of 1-naphthol in expt 14 and 16 shows that III undergoes demethylation at reaction conditions. Further, the formation of only trace amounts of 1-methoxy-2-methylnaphthalene (IV) and the absence of other products containing a methoxy group indicates that III is not methylated *per se*. More likely, III is first cleaved on the alumina surface (with or without the intervention of another chemical entity) to give I or its anion, which then reacts in the usual manner. The significantly lower conversion of III at 280–350° implies that the cleavage reaction of III is slow compared to methylation of I. Alternatively, but less likely, III may first rearrange to 2-methyl-1-naphthol in a step which proceeds at a slower rate than subsequent methylation.

Over catalyst A at 420°, the product compositions from III and I are nearly identical (*cf.* expt 18 and 19). This is consistent with the expected increase in the rate of cleavage or of rearrangement of III with increased catalyst acidity and higher temperature. It is apparent that at such conditions the preparation of methylnaphthalenes by the alumina-catalyzed methylation process can proceed with equal facility from either I or III as a substrate.

Experimental Section[11]

Apparatus, Catalysts, and Procedure.—The apparatus and experimental procedure were essentially the same as previously employed,[2] except that experiments were carried out on a smaller scale and the catalyst–substrate and methanol–substrate ratios were higher than those used in the study of 1-naphthol.[2] For each run 35 g of fresh alumina catalyst was used in the form of a bed 18 cm long and supported in the isothermal section of the reactor. In addition to the previously described catalysts A (from aluminum isopropoxide) and C (Houdry hard alumina)[2] a third alumina catalyst (D) was also used. D was prepared by solution of aluminum (99.9% pure) in aqueous potassium hydroxide, neutralization of excess alkali with nitric acid, and, finally, precipitation of aluminum hydroxide with carbon dioxide.[4] All catalysts were activated *in situ* as previously.[2] The influent consisted of a solution of III, IX, or X (0.012 mol) in methanol (20 g, 0.63 mol) and was introduced into the reactor at a uniform rate over a period of 2 hr. Products were processed and analyzed as before.[2]

Isolation and Identification of Reaction Products.—1-Naphthol, methylated 1-naphthols (V–VIIa), 1-methoxynaphthalene, and methylnaphthalenes (XII–XIV, XVI–XIX, XXI–XXIII) were identified by comparison of pmr and infrared spectra, as well as vpc retention volumes, with those of authentic samples.[2]

(11) Unless otherwise noted, analytical methods for vpc and for infrared and pmr spectra were the same as in ref 2. Ultraviolet spectra were measured by means of a Cary Model 11 spectrophotometer.

3,4-Dimethyl-1-naphthol (VIIb) was isolated by gas chromatography of the combined acidic fractions of several runs made under the conditions of expt 10. It was recrystallized from 80% ethanol: mp 121–122.5° (lit.[7] mp 120–122°); pmr spectrum (in $CDCl_3$), two singlets, 3 H each (δ 2.32, 2.45) methyl groups; broad singlet, 1 H (5.1) OH; singlet, 1 H (6.52) proton at C-2; multiplet, 4 H (7.1–8.3), aromatic protons at C-5 to C-8; $\nu_{max}^{CS_2}$ [intensities: (s) strong, (m) medium] 758 s, cm^{-1}, 838 m, 1081 m, 1087 m, 1151 m, 1226 s; $\nu_{max}^{CHCl_3}$ 1357 m cm^{-1}, 1366 m, 1390 s, 1464 m, 1521 m, 1600 s, 1630 m, 2945 m, 3030 m, 3610 s; identical in the spectral patterns with an authentic synthetic sample;[9] converted into 2-bromo-3,4-dimethyl-1-naphthol, mp 101–102° (lit.[9] mp 101.5–102.5°). The infrared absorption bands of VIIb at 758 and 838 cm^{-1} are assigned to CH out-of-plane deformation of the vicinal hydrogens in the unsubstituted ring and of the lone hydrogen at C-2, respectively.

1,1,3-Trimethyl-1,2-dihydronaphthalene (XXXIII) was isolated as a colorless liquid by preparative vpc from the products of expt 10 and 11: bp 249° (751 mm) by micromethod;[12] $n^{20}D$ 1.5536; pmr spectrum, singlet, 6 H (δ 1.22) geminal dimethyl group; broadened singlet, 3 H (1.86) vinylic methyl group; broadened singlet, 2 H (2.08) methylene group; broadened singlet, 1 H (6.13) vinylic proton; and multiplet, 4 H (6.7–7.3) aromatic protons; $\nu_{max}^{CS_2}$ 752 s cm^{-1}, 760 m, 843 m, 887 m, 1047 m, 1142 m; $\nu_{max}^{CCl_4}$ 1365 m cm^{-1}, 1447 s, 1489 s, 1662 m, 2920 m, 2980 s; λ_{max}^{EtOH} 263 mμ (log ε 4.10), 269 (4.11).

Anal.[13] Calcd for $C_{13}H_{16}$: C, 90.64; H, 9.36. Found: C, 90.31; H, 9.27.

The CH out-of-plane deformation of the four vicinal aromatic hydrogens of XXXIII shows a characteristic splitting (bands at 752 and 760 cm^{-1}). Similar doublets at *ca.* 735 and 753 cm^{-1} are observed in the spectra of 1,2,3,4-tetrahydronaphthalenes which possess an unsubstituted aromatic ring.[14] The similarity of the ultraviolet absorption spectrum of XXXIII to that of 1,2-dihydronaphthalene (partially resolved maxima at *ca.* 260 and 265 mμ, log ε *ca.* 4),[15] but shifted bathochromically by 3–4 mμ, is consistent with conjugation of the carbon–carbon double bond with the benzenoid ring and with the location of a methyl substituent on this double bond. The C=C stretching vibration at 1662 cm^{-1} corroborates these structural assignments since its position is normal for a conjugated, trisubstituted double bond (*i.e.*, ν somewhat less than 1670 cm^{-1}) and its intensity is enhanced compared to that of a nonconjugated double bond.[16]

Aromatization of XXXIII.—According to a general procedure,[17] a solution of 172 mg (1 mmol) of preceding XXXIII and 0.5 g (2.2 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone in 50 ml of dry benzene was refluxed for 5 hr. The reaction mixture was diluted with petroleum ether (bp 30–60°), filtered, and chromatographed on Woelm neutral alumina with petroleum ether–benzene (1:1 by vol) as eluent. Evaporation of the effluent left 162 mg (93%) of 1,2,3-trimethylnaphthalene, identified by direct comparison of its infrared spectrum and vpc retention volume with those of a reference sample.[2]

Reaction of 1-Oxo-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene (XXXVI) with Methanol.—A solution of 0.8 g of 1-oxo-4,4-dimethyl-1,2,3,4-tetrahydronaphthalene[9] [pmr spectrum, singlet (δ 1.30) geminal methyl groups; symmetric A_2B_2 multiplet centered at δ 2.23 ($\Delta\delta_{AB}$ = 39 cps, $J_{AB}/\Delta\delta_{AB} \simeq 0.2$)[18] dimethylene group; multiplet (6.9–7.6) aromatic protons probably at C-5 to C-7; multiplet (7.7–8.0) aromatic proton probably at C-8] in 8 g of methanol was passed over catalyst C at 320° under conditions identical with those in expt 10, Table II. Conversion of the ketone was 68%. The total reaction product (0.55 g, excluding starting materials) was found by vpc to contain 78% by weight of XXXIII, plus unidentified components.

1-Hydroxy-2,2-dimethyl-1,2-dihydronaphthalene (XXXII).—To a stirred solution of 0.85 g of 1-oxo-2,2-dimethyl-1,2-dihydronaphthalene[2] in ethanol was added (over a period of 10 min) a suspension of 0.1 g (excess) of sodium borohydride in the same solvent. The mixture was stirred for 2.5 hr, and the solvent was evaporated *in vacuo*. The residue was treated with water, left overnight, and then extracted with ether. Evaporation of the dried ether extract gave 0.84 g (97%) of viscous, colorless liquid, 98% pure as determined by vpc with a stationary phase of 550-DC silicone oil (10% by wt) on Chromosorb W at 150° and high helium flow rate (>200 cc/min). Preparative vpc gave a chromatographically pure sample: $n^{25}D$ 1.5665; pmr spectrum, two singlets, 3 H each (δ 0.95, 1.00) geminal methyl groups; broadened doublet, 1 H (δ 2.84, J = 6 cps) proton at C-1; broadened doublet, 1 H (δ 4.28, J = 6 cps) OH proton; AB system, 2 H (δ_A 5.62, δ_B 6.22, J_{AB} = 9.5 cps) vinylic protons at C-3 and C-4; multiplet 4 H (6.7–7.5) aromatic protons; $\nu_{max}^{CS_2}$ 697 m cm^{-1}, 751 m, 770 s, 779 s, 790 s, 836 m, 948 m, 999 s, 1027 m, 1048 s, 1360 m, 1376 s; $\nu_{max}^{CHCl_3}$ 1468 s, and 1487 s cm^{-1}; $\nu_{max}^{CS_2}$ 2878 m cm^{-1}, 2936 m, 2973 s, 3035 m, 3490 m, 3604 m.

Anal.[19] Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.91; H, 8.18.

Dehydration of XXXII on Alumina.—A solution of 0.6 g of XXXII in 6 g of methanol was passed (at constant rate over a period of 35 min) through a column containing 25 g of catalyst C at 350°. This was followed by 50 ml of benzene. The combined organic effluent was separated from water, dried, and evaporated to leave 0.5 g (93%) of 1,2-dimethylnaphthalene, free of isomers as based on vpc with a stationary phase of Bentone 34 (10% by wt) and 550-DC silicone oil (5%) on Chromosorb W; identical in infrared spectrum and vpc retention volume with a reference sample.

Registry No.—III, 2216-69-5; VIIb, 16020-34-1; IX, 16020-15-8; X, 16020-16-9; methanol, 67-56-1; XXXII, 16020-36-3; XXXIII, 16020-37-4; XXXVI, 2979-69-3.

Acknowledgment.—The authors wish to thank Dr. C. E. Klopfenstein of this laboratory for calculation of the HMO reactivity indices in Scheme III.

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(19) Analyzed by Micro-Tech Laboratories, Skokie, Ill.

Alumina-Catalyzed Reactions of Hydroxyarenes and Hydroaromatic Ketones. III. Reactions of 2-Methyl-, 4-Methyl-, and 2,4-Dimethyl-1-naphthols with Methanol. Sequential Pathways to Polymethylnaphthalenes[1a]

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The alumina-catalyzed reactions of methanol with 1-naphthol (I), 2-methyl-1-naphthol (V), 4-methyl-1-naphthol (VI), and 2,4-dimethyl-1-naphthol (VIIa) were studied under comparable conditions at 350–420°. Quantitative identity in the composition of methylnaphthalenes from I and V indicates that methylation of I at C-2 is a primary step with no major influence on the extent of subsequent substitution. The reactions of VI and VIIa are highly selective and give 1,2,4-trimethylnaphthalene and 1,2,4,7-tetramethylnaphthalene as main products (combined yields, 61–87 mol %). A general, sequential pathway is proposed for formation of polymethylnaphthalenes from 1-naphthols. Data on the composition of the total methylnaphthalene product from I at different reaction temperatures are used to estimate the relative over-all extents of ring methylation at C-2, C-4, and C-7.

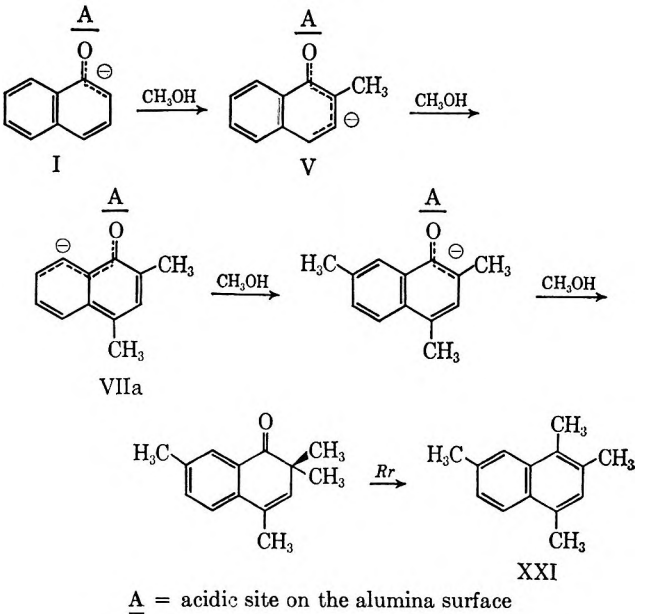
As an extension of research on alumina-catalyzed reactions of hydroxyarenes and hydroaromatic ketones,[2,3] a comparative study was made of the reactions of methanol with 1-naphthol (I), 2-methyl-1-naphthol (V), 4-methyl-1-naphthol (VI), and 2,4-dimethyl-1-naphthol (VIIa), respectively. The experimental and analytical procedures were essentially the same as described previously.[2,3] Reactions were carried out at two selected temperatures, 350 and 420°, over catalyst A (pure alumina, obtained by hydrolysis of aluminum isopropoxide) and catalyst C (Houdry hard alumina, which contains *ca.* 0.4% of sodium).[2-4] In the temperature range studied A is distinctly more acidic than C.[2,3]

As seen from Table I the composition of methylnaphthalene products formed by the reaction of V with methanol varies with reaction temperature and catalyst used. However, in all cases (expt 1–4) the di-, penta-, and hexamethylnaphthalene fractions consist only of one isomer each, *viz.* 1,2- (XIV), 1,2,3,4,6- (XXII), and (where present) 1,2,3,4,6,7- (XXIII), respectively. The yield of XIV is higher with catalyst C than with A, while yields of XXII and XXIII are higher with the more strongly acidic A. Three trimethylnaphthalenes, 1,2,3- (XVI), 1,2,4- (XVII), and 1,2,7- (XVIII), and two tetramethylnaphthalenes, 1,2,3,4- (XIX) and 1,2,4,7- (XXI), are also formed. Among the former XVIII is the major component with A (expt 3 and 4), whereas XVII predominates with C (expt 1 and 2). XXI is the major tetramethyl isomer with either catalyst. With A the composition of methylnaphthalene products from V is closely similar to that from I (*cf.* expt 3 and 11; 4 and 12). This result is consistent with previous observations that methylation of I produces V as the predominant isolable methylated naphthol under mild reaction conditions (275–350°)[2] and indicates that up to 420° methylation of I occurs more readily at C-2 than at any alternative ring position (*vide infra*).

On the other hand, the composition of methylnaphthalene products formed from 4-methyl-1-naphthol (VI) or 2,4-dimethyl-1-naphthol (VIIa) differs markedly from that produced from I or V. (a) No 1,2-dimethylnaphthalene is found, but the isomeric 1,3-dimethylnaphthalene is formed in small yield instead. (b) Only a single trimethylnaphthalene, *i.e.*, the 1,2,4 isomer (XVII), is produced. In fact, at 420° with the weakly acidic catalyst C (expt 5 and 9) the reaction can be conveniently employed as a preparative method for XVII (60–66 mol %). (c) Yields of 1,2,4,7-tetramethylnaphthalene (XXI) are notably higher from VI or VIIa (40 mol % at 420° with A, *cf.* expt 6 and 10), while yields of the pentamethyl (XXII) and hexamethyl (XXIII) compounds are slightly higher than those from I or V. Thus, the initial introduction into I of a methyl group at C-4 fosters the formation of 1,2,4-trimethyl- and 1,2,4,7-tetramethylnaphthalenes, while at the same time it completely inhibits the pathways to 1,2-dimethyl- and 1,2,7-trimethylnaphthalenes.

In Schemes I and II are depicted typical proposed pathways for the formation of methylnaphthalenes from reaction of methanol with 1-naphthol, as based

SCHEME I



A = acidic site on the alumina surface

(1) (a) This investigation was supported by Research Grants No. CA-5969 from the National Cancer Institute and No. GM 12730 from the National Institute of General Medical Sciences, U. S. Public Health Service. (b) On leave from the Department of Chemistry, Weizmann Institute of Science, Rehovoth, Israel. (c) Research Assistant, 1964–1967.

(2) Part I: L. H. Klemm, J. Shabtai, and D. R. Taylor, *J. Org. Chem.*, **33**, 1480 (1968).

(3) Part II: J. Shabtai, L. H. Klemm, and D. R. Taylor, *ibid.*, **33**, 1489 (1968).

(4) For simplicity, compounds and catalysts are designated by the same Roman numerals and capital letters, respectively, as used in part I.[2]

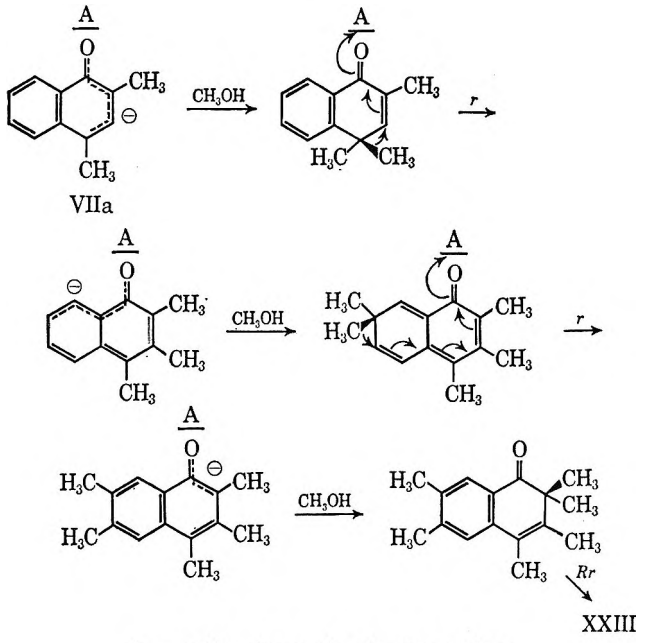
TABLE I

ALUMINA-CATALYZED REACTIONS OF 2-METHYL-1-NAPHTHOL (V), 4-METHYL-1-NAPHTHOL (VI), AND 2,4-DIMETHYL-1-NAPHTHOL (VIIa) WITH METHANOL[a]

Expt no.	1	2	3	4	5	6	7	8	9	10	11[b]	12[b]
Starting naphthol	V	V	V	V	VI	VI	VIIa	VIIa	VIIa	VIIa	I	I
Catalyst	C	C	A	A	C	A	C	A	C	A	A	A
Reaction temp, °C	350	420	350	420	420	420	350	350	420	420	350	420
Conversion,[c] mol %	65	98	76	100	100	100	86	95	100	100	87	100
Product component,[d] mol %												
1,2-Dimethyl-N[e] (XIV)	23.5	30.5	18.2	15.7	...	...	...	...	...	...	18.0	15.5
1,3-Dimethyl-N	...	...	...	...	1.3	1.1	4.5	3.4	1.5	1.5	...	...
1,2,3-Trimethyl-N (XVI)	1.7	1.9	4.6	4.0	...	...	...	...	...	...	4.5	4.0
1,2,4-Trimethyl-N (XVII)	8.4	12.5	5.2	5.8	60.3	22.4	51.0	36.1	66.2	20.3	5.3	5.7
1,2,7-Trimethyl-N (XVIII)	6.0	10.4	8.5	18.2	...	...	...	...	...	...	8.2	18.0
1,2,3,4-Tetramethyl-N (XIX)	1.4	3.0	3.2	3.0	2.2	1.9	2.5	2.9	1.6	2.4	3.6	3.1
1,2,4,7-Tetramethyl-N (XXI)	7.2	12.6	8.0	15.8	20.1	39.4	12.3	29.2	20.4	40.3	7.9	15.5
1,2,3,4,6-Pentamethyl-N (XXII)	3.2	8.1	10.5	18.4	8.6	20.1	3.6	10.8	9.2	21.0	10.2	18.7
1,2,3,4,6,7-Hexamethyl-N (XXIII)	...	Trace	1.4	5.5	0.1	6.6	...	1.6	0.2	7.5	1.3	5.6
Others	10.3	9.5	9.8	9.2[f]	1.0	7.7[g]	...	1.5	...	6.0[h]	22.0[i]	9.5[j]
Unidentified[k]	(3.5)	(9.0)	(4.8)	(3.0)	(4.4)	(0.5)	(11.7)	(8.5)	(0.5)	(0.6)	(4.5)	(3.5)

[a] A mixture of 0.0125 mol of the naphthol and 20 g (0.63 mol) of methanol was used as starting material in each experiment. This solution was introduced into the reactor at a uniform rate during a period of 2 hr. [b] Small changes from previous data[2] in the composition of products formed are ascribed to differences in the naphthol–catalyst and the naphthol–methanol ratios used. [c] Conversion of the naphthol. [d] Calculated on the basis of 100 mol of starting naphthol (including unreacted material). Differences between conversion and total products formed represent losses due to unrecoverable deposits on the catalyst. [e] N is naphthalene. [f] Includes 3.8 mol % of heptamethylnaphthalene (XXIV) and 1.7 mol % of octamethylnaphthalene (XXV), as based on gas chromatographic data only. [g] 1-Methylnaphthalene, 2.0; XXIV, 3.9; and XXV, 1.8 mol %. [h] XXIV, 3.9; XXV, 2.1 mol %. [i] Includes 10.6 mol % of V. [j] Includes XXIV, 3.8; XXV, 1.9 mol %. [k] Percentage by weight of total product. It includes unidentified chromatographic peaks and nondistillable residues.

SCHEME II



A = acidic site on the alumina surface

on the data reported in preceding papers[2,3] and the results of the present study. It is assumed that all oxygen-containing species are adsorbed on the surface of the alumina catalyst where methylation by an electrophilic species and processes of molecular rearrangement (*r*) and reduction–rearrangement (*Rr*) occur. For simplicity all naphtholic compounds are represented as anions (adsorbed to acidic sites) and the pertinent electromeric shift involved in each step of ring methylation is shown. For each naphthoxide ion there is a corresponding proton adsorbed to a basic site (not shown). Methylation is accompanied by the over-all loss of water. The oxygen function is considered to be the anchoring group for adsorption, but adsorbability should be enhanced by simultaneous flatwise orientation of the aromatic system with attendant interaction of the π-electronic system with the polarizing surface. If the methylating species is confined to the surface layer, such flatwise adsorption would be essential for methylation at positions other than C-2. Methylnaphthalenes formed would be largely displaced from the catalyst surface by the more strongly adsorbed oxygen-containing entities (including methanol).

As indicated in Schemes I and II ring methylation proceeds stepwise, without loss of the oxygen function, at C-2, C-4, and C-7 positions which are favored for electrophilic substitution and are not sterically hindered.[2] Insertion of a second methyl group at C-4 or at C-7 is followed by rearrangement to 3,4-dimethyl[5] and 6,7-dimethyl derivatives, respectively (Scheme II). On the other hand, insertion of a second methyl group at C-2 terminates the methylation process with the formation of a 1-oxo-2,2-dimethyl-1,2-dihydronaphthalene derivative. Compounds of this type serve as immediate precursors of the final methylnaphthalene products by undergoing elimination of the keto oxygen and migration of one of the geminal methyl groups from C-2 to C-1. Possible, detailed mechanisms for the methylation, reduction, and rearrangement processes were considered previously.[2,3] The average number of methyl substituents introduced into the naphthalene system depends on the reaction temperature, the catalyst acidity, and the methanol–naphthol ratio used.[2] For an individual naphthol molecule the exact number of substituents may depend on the strength of the particular acidic site to which the substrate is adsorbed, on the orientation of the ring system relative to the catalyst surface, and finally on the proximity and orientation of the methylating species.

Only one sequential pathway (that of dimethylation at C-2 followed by reduction–rearrangement, *Rr*) is visualized for formation of XIV. This sequence is represented by the notation 2,2,*Rr*, where the numbers refer to the positions of methylation on the ring. Two pathways, either successive methylations at C-2, C-4, C-2 or at C-4, C-2, C-2 and then reduction–

(5) Reference 3, Scheme IV.

rearrangement are possible for formation of XVII. These alternatives are symbolized by (2,4),2,*Rr*, where the numbers in parentheses refer to allowed permutations in the methylation sequence. Analogously, two routes (2,7),2,*Rr* would lead to XVIII. As the depth of methylation increases the number of possible pathways increases markedly. Thus, there are three routes 4,4,*r*,2,2,*Rr* and (2,4),4,*r*,2,*Rr* to XIX; six routes (2,4,7),2,*Rr* to XXI; 12 routes 4,4,*r*(2,7),2,*Rr*, (2,4),-4,*r*,7,2,*Rr*, (4,7),4,*r*,2,2,*Rr*, and (2,4,7),4,*r*,2,*Rr* to XXII; and 30 routes to XXIII. Each route involves the common steps of . . .2,. . .,2,*Rr*, *i.e.*, methylation at C-2 at some preceding stage, a second methylation at C-2 at a penultimate stage, and finally reduction–rearrangement to 1,2-dimethylnaphthalene or its ring-methylated derivative. Thus, the process 2,2,*Rr*, which leads to XIV, may be considered the simplest typical route. The observation that 1-oxo-2,2-dimethyl-1,2-dihydronaphthalene (IX) is almost exclusively converted into XIV under reaction conditions[3] is consistent with this pathway. Moreover, the selective conversion of 1-oxo-4,4-dimethyl-1,4-dihydronaphthalene (X) into XIX and XXII[3] lends credence to the pathways 4,4,*r*,2,2,*Rr* and 4,4,*r*,(2,7),2,*Rr*. On the other hand, the main route to XIX from I is probably 2,4,4,*r*,2,*Rr* and that to XXII is probably 2,(4,7),4,*r*,2,*Rr* or 2,4,4,*r*,7,2,*Rr* (or a combination of these). There are nine methylnaphthalenes which might be expected on the basis of the foregoing general pathways. These correspond to all possible combinations for the introduction of zero–two methyl groups at each of the positions C-4 and C-7. Products XIV, XVII–XIX, and XXI–XXIII correspond to seven of these possibilities. The remaining two should be 1,2,6,7-tetramethylnaphthalene (from dimethylation at C-7 but no methylation at C-4) and 1,2,4,6,7-pentamethylnaphthalene (from dimethylation at C-7 and monomethylation at C-4). Vpc analysis of mixed methylnaphthalene products failed to reveal the presence of a second pentamethylnaphthalene, in addition to the 1,2,3,4,6 isomer (XXII) found. However, a third, unidentified tetramethylnaphthalene, in addition to the 1,2,3,4 (XIX) and 1,2,4,7 (XXI) isomers, was readily detected by this method. Tentatively, this isomer (XX) has been assigned the 1,2,6,7-substitution pattern[6] on the basis of the preceding mechanistic considerations.

Whereas most of the lower precursors required by the proposed mechanism, *i.e.*, compounds V–X, were isolated from the products at 275–300°,[2] only very small amounts (*ca.* 1% by weight) of the precursors of higher methylnaphthalenes are indicated at this mild temperature. The formation of such intermediates apparently requires somewhat higher temperature, where conversion into methylnaphthalenes is fast. Chromatograms of the products obtained at 300–350° showed a number of small peaks in the range of tri- and tetramethylnaphthalenes. Since a preparative sample enriched in these minor components gave carbonyl absorption in the infrared region (*ca.* 1690 cm^{-1}), it is possible that these peaks are due to the higher precursors.

On the basis of the proposed general mechanism it is possible to approximate the relative over-all extents of methylation of 1-naphthol at C-2, C-4, and C-7 by calculating the total number of substituents at C-1 plus C-2, C-3 plus C-4, and C-6 plus C-7, respectively, in all product components.[6] For example, over catalyst A, at 300° the ratio of over-all methylation at the 2, 4, and 7 positions found by this method is 1.0:0.2:0.02; at 350° the corresponding ratio is 1.0:0.36:0.20; at 420° it is 1.0:0.46:0.31; and at 470° it is 1.0:0.31:0.35. The change in the ratios reflects the gradual increase in the extent of methylation at C-4 and C-7 relative to that at C-2 up to 420°, a temperature at which maximal depth of methylation is attained. A possible cause for the decrease in relative extent of methylation at C-4 above 420° is that enhanced thermal out-of-plane and in-plane deflections of the hydrogen at C-5 may sterically hinder approach of the methylating agent to the *peri* (*i.e.*, to the C-4) position.[7]

The importance of *peri* interactions in the methylation of naphthols is illustrated by the practical absence of substitution at C-5 and C-8 in the reactions of I, V, VI, and VIIa. Lack of methylation at the 5 position is especially significant in view of the higher calculated superdelocalizability for electrophilic attack at C-5 than at C-7 in I.[2] At 275–350° neither 5- nor 7-methyl-1-naphthol is formed from I. On the other hand, the lack of reaction at C-5 at higher temperature (350–550°) where polymethylation, including attack at C-7, takes place can be essentially attributed to the steric interference of a methyl substituent[7] introduced at C-4 in an earlier step.

The results of the reactions of 4-methyl-1-naphthol (VI) and 2,4-dimethyl-1-naphthol (VIIa) are fully consistent with the proposed mechanism. Since methylation occurs to a lesser over-all extent at C-4 than at C-2 (for the initial precursor I), the preliminary introduction of a methyl substituent at the former position facilitates the formation of 1,2,4-trimethylnaphthalene (XVII) and 1,2,4,7-tetramethylnaphthalene (XXI). At the same time the presence of the 4-methyl group in VI and VIIa excludes the possibility of reaction sequences leading to 1,2-dimethyl- and 1,2,7-trimethylnaphthalenes. The formation of XVII as main product in expt 5 and 9 indicates that over the weakly acidic catalyst C at 420° a *second* methylation of VI or VIIa at C-2 occurs to a larger extent than a second methylation step at C-4 or than a first one at C-7. On the other hand, the high yield of XXI in expt 6 and 10 shows that in the presence of the strongly acidic catalyst A at 420° methylation occurs to a large extent at C-7 prior to a second (terminal) methylation at C-2. With 1-oxo-4,4-dimethyl-1,4-dihydronaphthalene (X) as substrate[3] over A, the gradual change with temperature of relative over-all extent of methylation at C-2 and C-7 (as based on comparison of yields of XIX, XXII, and XXIII) can also be noted. The ratios of methylation at the 2 and 7 positions, in this case, are 4.9:1 at 320°, 3.6:1 at 350°, 2.3:1 at 375°, and 2.0:1 at 420°.

It was shown previously[6] that for reaction of I below 420° values for average depth of ring methylation and for mole percentage conversion are higher with the pure alumina catalyst A than with the sodium-containing catalysts B or C. These gross differences probably arise from a higher concentration of strongly acidic sites on the surface of A than on either of the other

(6) Reference 2, Table I.

(7) V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

catalysts.[8,9] At 420–470°, however, these values tend to converge for catalysts A and C. A marked increase in the catalytic activity of alumina for hydrocarbon reactions has been observed to occur above 400° and has been ascribed to the conversion of passive acidic sites into active ones.[10] In the present case the production of active sites for the methylation process may be especially large on catalyst C for temperatures above 400°. However, it should be noted that A, B, and C do not show equivalent catalytic properties even in this temperature range, since differences in the distribution of methylated naphthalenes and in isomeric compositions still persist.[6] This may be due to nonequivalence in the nature and geometric arrangements of active sites on A and C, with attendant differences in orienting influences on the adsorbed substrates.

The formation of several minor product components, *viz.* naphthalene (XI), 1-methylnaphthalene (XII), 2-methylnaphthalene (XIII), 2,7-dimethylnaphthalene (XV), and 1,2,3-trimethylnaphthalene (XVI), cannot be accounted for by the proposed general mechanism. Direct reduction of the naphtholic group in I, VI, and V would, however, lead to XI, XII, and XIII, respectively. In fact XII (free from XIII) was found as a minor product from VI (Table I, footnote *g*). The small yield of 1,3-dimethylnaphthalene from 2,4-dimethyl-1-naphthol (expt 7 and 8) indicates that the same type of reaction occurs. Analogously XV could be derived from an intermediate 2,7-dimethyl-1-naphthol (not experimentally detected). The low yields of XI–XIII and XV from reactions of I[2] up to 550° imply that sequential methylation steps proceed in preference to direct reduction of the naphtholic group. A different pathway is likely for the formation of XVI, which is the main by-product in the reaction of methanol with 1-oxo-2,2-dimethyl-1,2-dihydronaphthalene (IX).[3] As noted previously IX may be methylated at C-3 before reduction–rearrangement occurs.[3]

(8) H. Pines and W. O. Haag, *J. Amer. Chem. Soc.*, **82**, 2471 (1960).
(9) J. B. Peri, *J. Phys. Chem.*, **69**, 231 (1965).
(10) S. E. Tung and E. McIninch, *J. Catal.*, **3**, 229 (1964).

Experimental Section

Apparatus, Materials, and Procedure.—The apparatus and experimental procedure were essentially the same as described previously.[2,3] For each run 35 g of fresh alumina catalyst (A, from aluminum isopropoxide; or C Houdry hard alumina)[2] was employed and the methanol–naphthol molar ratio was 50:1 (methanol, 0.63 mol; naphthol, 0.0125 mol). The methylnaphthols V, VI, and VIIa (about 99% pure, as based on chromatographic analysis) were synthesized by the methods given previously.[2] Product components (Table I) were isolated by gas chromatography and were identified by comparison of their pmr and infrared spectra, as well as their relative chromatographic retention volumes, with those of pure reference samples.[2] Gas chromatographic analysis of methylnaphthalene products was effected by means of a modified Bentone-34 column; and that of acidic (naphtholic) fractions, by means of Bentone-34 and Carbowax 20M columns.

Registry No.—Methanol, 67-56-1; I, 90-15-3; V, 7469-77-4; VI, 10240-08-1; VII, 4709-20-0.

Electrophilic Substitution in Acenaphthene and Related Compounds. I. Monobromination

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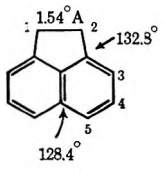
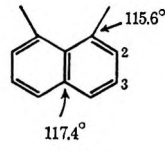
Isomer distribution in the bromination of acenaphthene has been determined for a variety of conditions and reagents. A wide variation was found in the per cent of *ortho* product. Isomer distributions for 1,8-dimethylnaphthalene, perinaphthane, and pleiadane were similar to those for acenaphthene using similar procedures.

There has been considerable recent interest[2-6] in the reactions of acenaphthene (1) and the related 1,8-dimethylnaphthalene (2). Electronic considerations suggest electrophilic attack would lead to a mixture of 3- and 5-substituted acenaphthenes or the corresponding 2- and 4-substituted 1,8-dimethylnaphthalenes.



1



2

Molecular dimensions[7,8] suggest that substitution *ortho* to the ethylene bridge in acenaphthene might not be as sterically hindered as 2-substitution in 1,8-dimethylnaphthalene.

Whereas it has been known[9] that reasonable (approximately 20%) yields of 3-nitroacenaphthene can be separated from 5-nitroacenaphthene after the treatment of acenaphthene with nitric acid in acetic anhydride, until recently no investigation had been made into isomer proportions in monosubstitution reactions of acenaphthene. Electrophilic substitution in 1,8-dimethylnaphthalene has been assumed to enter the 4

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(2) E. Berliner, D. M. Falcione, and J. L. Riemenschneider, *J. Org. Chem.*, **30**, 1812 (1965).
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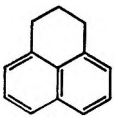
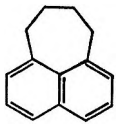
position.[2,10,11] An infrared investigation[6] has recently been made of the reaction products in the halogenation of acenaphthene in methanol and in 90% acetic acid, but some polyhaloacenaphthenes may also have been present.

Accurate information on isomer proportions in monosubstitution reactions of **1** and **2** is needed since the products reported to be isolated on disubstitution (either by further reaction on the hydrocarbon or by subsequent reaction with an already isolated monosubstituted compound) are sometimes unexpected on electronic and steric considerations. For example, such considerations would suggest that a 5-haloacenaphthene would undergo further electrophilic substitution at the 8 position. However, 5-chloroacenaphthene is reported[9] to yield considerable amounts of the 3-nitro compound on treatment with nitric acid in acetic anhydride, to chlorinate[12] in the 6 position, and to acylate[13] in the 3 and 8 positions. 5-Bromoacenaphthene is reported[9,13] to give a 28% yield of the 3-nitro derivative when treated with nitric acid in acetic anhydride but to afford[3] the 6-nitro derivative when nitrated in acetic acid, to brominate[14] in the 3 position, and acylate[13] in the 3 and 8 positions. 5-Iodoacenaphthene is reported[15] to iodonate further in the 3 position. All these results are based on product isolation and the intermediate 5-haloacenaphthene was not always isolated in the dihalogenation reactions. No results appear to be available for further substitution in 3-haloacenaphthenes. The bromination[16] of 4-bromo-1,8-dimethylnaphthalene apparently gives only 2,4-dibromo-1,8-dimethylnaphthalene.

We are at present undertaking a detailed investigation into this situation and the recent report[6] of a few results on the halogenation of acenaphthene prompts us to report our own rather more detailed study on the bromination of acenaphthene, 1,8-dimethylnaphthalene, perinaphthane[17] (**3**) and pleiadane[18] (**4**). Further investigations are in progress on disubstitution reactions and on the π electron distribution in acenaphthene.



3



4

Results and Discussion

We chose to investigate bromination because the reagents and conditions are relatively easy to standardize and the products can be analyzed by vapor phase chromatography. Since a considerable number of entities have been used as brominating reagents and solvents employed, we investigated a range of such procedures using acenaphthene. We kept the initial concentrations of acenaphthene and brominating species approximately constant throughout to aid comparison. Conditions were such that only part of the acenaphthene was brominated and disubstitution was detected in only one case. Results are shown in Table I in which the *ortho* product (3-bromoacenaphthene) is shown as a percentage of the total monosubstituted material. We found no evidence for 4 substitution, in agreement with previous workers,[6] but tests with authentic 4-bromoacenaphthene indicated it had a similar retention time to the 5-bromo isomer and trace amounts would thus not be detected by our procedure. However, any such small amounts would hardly affect our results.

TABLE I

BROMINATION OF ACENAPHTHENE[a] AT 20°

Condition	Brominating agent	Solvent	% *ortho* product in monobromination
1	Br_2	HOAc	3.4[b]
2	$BrPy_2OAc$	HOAc–Py	3.6
3	Br_2	Py	4.9
4	NBS	DMF	5.0
5	$BrPy_2NO_2$	Py	5.9
6	Br_2	CH_3NO_2	5.9[c]
7	Br_2	DMF	6.3
8	Br_2	CCl_4	8.1[d]
9	BrOAc	CCl_4	9.5
10	IBr	CCl_4	10.6
11	HOBr	25% aqueous HOAc	24.0[e]
12	HOBr	25% aqueous dioxane	32.4

[a] Acenaphthene, 0.005 mol; brominating species, 0.0025 mol. [b] Not significantly changed by trace amounts of added iodine or water. [c] Contained a trace amount of iodine. [d] Not significantly changed by a trace amount of added iodine. [e] Some disubstitution detected. Run contained either 0.23 mol of perchloric acid or 0.02 mol of sodium acetate and gave comparable results.

The results show a variation in per cent of *ortho* product from 3.4% with bromine in acetic acid to 32.4% with hypobromous acid in aqueous dioxane. This marked dependence of product composition on reagents and solvents used may be useful to help choose the best conditions for avoiding or aiding *ortho* attack in related compounds (but see below).

Our results from bromination of acenaphthene with hypobromous acid in acetic acid are somewhat less meaningful than the others in Table I since not all the acenaphthene immediately dissolved and some dibromination resulted. Similar results obtained in an acetate buffer or in the presence of perchloric acid are interesting, nevertheless, since the percentage of *para* bromination in diphenyl has been reported[19] to change from 46% (0.2 *M* perchloric acid) to 79% (0.02 *M* sodium acetate) under these conditions.

Further comments on some of the brominations are pertinent. Nitromethane was chosen since the chlorination of toluene in this solvent is reported[20] to give the lowest percentage (34%) of *ortho* chlorotoluene in a series of reactions with molecular chlorine in various media. In acetic acid a considerably larger (60%) yield of the *ortho* isomer was obtained. Our figures show the opposite order. N-Bromosuccinimide, which is more usually employed for the side chain bromination

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(17) 2,3-Dihydrophenalene.
(18) 7,8,9,10-Tetrahydrocyclohepta[*d*,*e*]naphthalene.
(19) P. B. de la Mare and J. L. Maxwell, *J. Chem. Soc.*, 4829 (1962).
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of alkyl aromatics in the presence of a radical initiator such as benzoyl peroxide, can also be used[21] for nuclear bromination in polar solvents. It has been suggested[22] to be a source of bromonium ions when used in dimethylformamide. However, our results suggest that the brominating agent is likely to be molecular bromine rather than a positive species.

We selected conditions 1, 4, 8, and 12 (Table I) as being representative and used these for similar product ratio studies on 1,8-dimethylnaphthalene (2), perinaphthane (3), and pleiadane (4). The results are summarized in Table II.

TABLE II
COMPARISON OF THE PERCENTAGE *ortho* BROMINATION UNDER VARIOUS CONDITIONS AT 20°

Conditions (Table I)	Compd 1	2	3	4
1	3.4	4.4	4.0	5.3
4	5.0	6.3	3.6	5.5
8	8.1	4.6	6.4	5.3
12	32.4	29.8	38.8	38.4

Surprisingly, compounds 2, 3, and 4 show little variation in percentage *ortho* bromination under the first three conditions. The amount of the *ortho* isomers obtained with hydrobromous acid in aqueous dioxane (condition 12) is remarkably high in relation to the expected increase in steric hindrance to such substitution. Some increase in strain in the transition state for *para* substitution would be expected in 2, 3, and 4 compared to acenaphthene (1) because of interaction with the *peri* hydrogen and this may partly offset the effect at the *ortho* position.

We also ran competitive experiments with pairs of compounds to compare rates of bromination. The percentage of isomeric products was not significantly altered for any one compound in the presence of another. Considering the total amount of monobromination and arbitrarily assigning a rate of unity to perinaphthane we found that the rates of bromination in acetic acid (condition 1) were acenaphthene > perinaphthane > pleiadane > 1,8-dimethylnaphthalene in the ratio 9.74 > 1.00 > 0.56 > 0.24. A similar order was obtained for condition 12 in the ratio 3.18 > 1 > 0.66 > 0.46. The more selective brominating conditions gave a greater spread as expected.

Experimental Section

Reagents.—Acenaphthene (mp 96°), 1,8-dimethylacenaphthene (mp 61–62°), perinaphthane[23] (mp 64.5°), and pleiadane[24] (mp 57–58°) were recrystallized samples tested for purity by vpc.

The hydrocarbon (0.04 mol) in acetic acid (200 ml) was allowed to react with bromine (0.04 mol) in acetic acid (50 ml) over 6 hr with stirring at room temperature in the absence of light. The mixture was poured into water (500 ml) and the mixture then extracted with three 25-ml portions of benzene. The benzene layer was washed with water and dried over anhydrous sodium carbonate. Distillation under reduced pressure followed by recrystallization from pentane–ethanol gave 5-bromoacenaphthene,[25] mp 53–53.5° (*Anal.*[26] Calcd for $C_{12}H_9Br$: Br, 34.33. Found: Br, 34.52); 4-bromo-1,8-dimethylnaphthalene,[10] mp 31–31.5° (*Anal.* Calcd for $C_{12}H_{11}Br$: Br, 34.04. Found: Br, 33.76); 6-bromoperinaphthane, mp 24–25° (*Anal.* Calcd for $C_{13}H_{11}Br$: Br, 32.40. Found: Br, 32.62); 7-bromopleiadane, mp 26.5–27°) (*Anal.* Calcd for $C_{14}H_{13}Br$: Br, 30.66. Found: Br, 30.65).

Authentic samples of 3- and 4-bromoacenaphthenes and 3-bromo-1,8-dimethylnaphthalene were available from other work.[10,25]

Bromine, acetic acid, carbon tetrachloride, dimethylformamide, dioxane, pyridine, and nitromethane were purified by standard methods and fractionated before use. Iodine monobromide was a commercial sample titrated against sodium thiosulphate. Bromine dipyridine nitrate[27] had mp 76–77°. Bromine dipyridine acetate was prepared[28] in solution before use.

Bromination.—The general procedure (conditions 1–8, 10) was to place the hydrocarbon (0.005 mol) in 10 ml of the chosen solvent in a reaction vessel containing the brominating entity (0.0025 mol in 5 ml of solvent) in a second chamber. The vessel was immersed in a thermostated bath at 20° for 20 min and the brominating solution then added to the stirred hydrocarbon solution over 30 min. Reaction was continued for a further 30 min. The contents of the reaction vessel were then shaken with benzene (20 ml) and sodium sulfite solution (10 ml, 10%). The benzene layer was washed with water and dried over anhydrous sodium carbonate, and the solvent was evaporated. The residue was analyzed by vpc. Three experiments were conducted for each set of conditions and three vpc analyses made on each product. The results shown in Table I represent the average values of the nine determinations for each, but significant variation was not found in individual analyses. Bromine acetate (condition 9) was prepared[29] by adding bromine (1 ml) in carbon tetrachloride (20 ml) over 30 min to a suspension of silver acetate (4 g) in the same solvent (160 ml). The mixture was then shaken for 90 min and the precipitated silver bromide removed. The solution was titrated against sodium thiosulfate. The bromine acetate solution (0.0025 mol, 25 ml) was added to acenaphthene (0.005 mol) in carbon tetrachloride (25 ml) and the reaction otherwise was carried out as above.

The hypobromous acid solution for runs 11 and 12 was prepared from bromine, water, and silver sulfate and distilled under reduced pressure. It was standardized against sodium thiosulfate. The acenaphthene (0.005 mol) was dissolved in 75 ml of the chosen solvent and the hypobromous acid (0.0025 mol) made up to 100 ml. The acenaphthene was not completely dissolved initially when acetic acid was used and the reaction mixture was therefore allowed to stand overnight before the products were isolated. Some dibromination was detected (vpc). The acenaphthene was completely dissolved when dioxane was used as a solvent and no dibromination occurred.

Gas Chromatography.—A Pye "Argon" gas chromatograph with an Sr-90 ionization detector was used for the analyses. The columns were packed with 10% poly(ethylene glycol) adipate or 7.5% polyethylene adipate–2.5% Apiezon L (for bromo-1,8-dimethylnaphthalenes) and used at a temperature of 175°. The products from the bromination of each hydrocarbon gave three peaks. The first peak was readily identified as unchanged hydrocarbon. The compound corresponding to the third and major peak was isolated and shown to be a monobromo hydrocarbon in each case, and further identified with the known 5-bromoacenaphthene and 4-bromo-1,8-dimethylnaphthalene in these instances. The generally small intermediate peak obtained in the bromination of acenaphthene was identified with an authentic sample of 3-bromoacenaphthene and the other intermediate peaks assumed to be the corresponding *ortho* isomers by analogy and by noting their marked increase in each case when hypobromous acid was used as a brominating agent. Authentic samples of 4-bromoacenaphthene and 3-bromo-1,8-dimethylnaphthalene had longer retention times than the minor peaks obtained in the

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bromination of the corresponding hydrocarbons. It was also shown that side chain brominated products produced by use of N-bromosuccinimide in carbon tetrachloride in the presence of benzoyl peroxide, gave peaks with different retention times. (1-Bromoacenaphthene decomposed on the column to give acenaphthylene.)

The chromatograph was calibrated directly with mixtures of the hydrocarbons and their *para* bromo derivatives and with 3-bromoacenaphthene. It was shown that 3- and 5-bromoacenaphthenes gave equal responses and equivalent result for the other pairs of bromo isomers was shown by checking the results with a gas chromatograph with a gas density balance as a detector.

Registry No.—**1**, 83-32-9; **2**, 569-41-5; **3**, 479-58-3; **4**, 14622-16-3; 6-bromoperinaphthane, 15733-72-9; 7-bromopleiadane, 15733-73-0.

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The Kinetic Isotope Effect in the Formation of Anthraquinone[1,2]

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The rate of formation of anthraquinone from 2-(2′-deuteriobenzoyl)benzoic acid is less than the rate for the protium analog, k_H/k_D varying from 1.28 in 97% sulfuric acid to 1.20 in 104% sulfuric acid. The product anthraquinone retains from 56 to 62% of one deuterium. The mechanistic implications of these results are discussed.

Isotope effects in aromatic substitution processes have been examined for many reactions by two different approaches. On the one hand there are direct comparisons of the rate of reaction of a protium compound and of its deuterium analog. Many examples typically show little or no isotope effect.[4] For example, in the nitration of nitrobenzene-d_5[5] k_H/k_D is 1.0 to within about 5%; similar results have been reported by De la Mare, Dunn, and Harvey[6] for the bromination of benzene and benzene-d_6. In other situations, however, there is observed a substantial deuterium isotope effect ($k_H/k_D \gg 1$). These situations have been characterized as ones in which the removal of the aromatic hydrogen is achieved by a general base in the rate-limiting step.[7,8] In still other cases intermediate values for k_H/k_D have been obtained. These results have been interpreted as indicating that the rate of proton loss from the Wheland intermediate is of about the same magnitude as the reversal of the attack of the substituting species upon the aromatic compound.[9]

The secondary isotope effects which accompany the formation of the Wheland intermediate are generally small. Berliner and Schueller[10] have concluded that in the bromination of biphenyl the formation of the Wheland intermediates is rate limiting with a secondary effect of $k_H/k_D = 1.15$. More recently Helgstrand and Lamm[11] have observed that the secondary isotope effect in the azo coupling reaction of *p*-chlorobenzenediazonium ion with trimethoxybenzene is inverse, $k_T/k_H = 1.13$. Very recently Kresge and Chiang[12] also reported an inverse secondary isotope effect in the aromatic hydrogen exchange of trimethoxybenzene, $k_H/k_D = 0.90$. Streitwieser[13] has pointed out that only modest secondary effects are to be expected in the formation of the Wheland intermediate as a result of the counterbalancing influences of the change in hybridization and of hyperconjugation. The results of Kresge and Chiang[12] and of Helgstrand and Lamm[11] suggest that the resultant of these influences will generally be a very small inverse effect. This is consistent with the results of Batts and Gold.[14]

Particularly pertinent to the present discussion are the results of Schubert and his students on the mechanism of the decarbonylation of aromatic aldehydes[15] which showed that proton attack on the aromatic ring of mesitaldehyde or of 2,4,6-triisopropylbenzaldehyde was not solely the rate-limiting step, but that the decomposition of the Wheland intermediate was partly rate limiting. Evidence for this was adduced from the observed isotope effect with mesitaldehyde-α-d and the solvent isotope effect.

There are studies of deuterium isotope effects in aromatic acylation reactions of the Friedel–Crafts type, which have been of the second-type, competitive experiments. Denney and Klemchuk[16] have reported that the cyclization of 2-(2′-deuteriophenyl)benzoic acid to fluorenone under a variety of conditions shows an isotope effect as measured by the deuterium content of the product. Jensen has reported[17] that benzene-d_6 is benzoylated 1.6 times more slowly than benzene; that toluene-4-d_1 shows k_H/k_D of 2.4 on benzoylation in

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(2) Supported in part by Grants G-13125 and GP-1572 from the National Science Foundation.

(3) National Science Foundation Cooperative Graduate Fellow, 1961–1962; National Institutes of Health Predoctoral Fellow, 1962–1963.

(4) It is not the purpose of this discussion to attempt to present a comprehensive review. For leading references and an excellent discussion the reader is referred to the reviews by Melander ("Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960), by Zollinger ("Advances in Physical Organic Chemistry," Vol. II, V. Gold, Ed., Academic Press Inc., New York, N. Y., 1964, pp 163–200), and by Halevi ("Progress in Physical Organic Chemistry," Vol. I, S. G. Cohen, A. Streitwieser, Jr., and R. W. Taft, Ed., Interscience Publishers, Inc., New York, N. Y., pp 109–221).

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benzoyl chloride solution; and that there is a kinetic isotope effect in the benzoylation of naphthalene.

In order to gain more insight into the later stages of the conversion of *o*-benzoylbenzoic acid into anthraquinone we have determined both the kinetic isotope effect and the product composition for the cyclization of 2-(2′-deuteriobenzoyl)benzoic acid under a variety of conditions.

Experimental Section[18]

2-Deuteriochlorobenzene.—In a 1-l., three-necked, round-bottomed flask, equipped with a pressure-equalized addition funnel, a stirring bar, and a condenser, was placed 28 g of magnesium turnings. The entire system was flushed carefully with dried nitrogen while warming. Through the third neck, ether (50 ml) dried over lithium aluminum hydride, was distilled directly into the flask. To complete the drying process 10.9 g, of ethyl bromide was added slowly. The remainder of the ether (500 ml) was distilled in and 191 g of *o*-bromochlorobenzene[19] was added slowly. After an additional 1 hr of stirring at room temperature, deuterium oxide (50 g) was added dropwise and cautiously. Working up in the usual fashion afforded 57.3 g (50%) of pure 2-deuteriochlorobenzene: bp 129–130° (spinning-band column), n^{20}D 1.5237 (lit.[20] bp 129.7–130.4°, n^{25}D 1.5210.

2-(2′-Deuteriobenzoyl)benzoic Acid.—The Grignard reagent was prepared from 8.75 g of magnesium and 37.5 g of 2-deuteriochlorobenzene in 75 ml of tetrahydrofuran following the procedure of Ramsden, *et al.*[21]

Occasional heating was required to maintain the reaction. The clear brown solution of 2-deuteriophenylmagnesium chloride was diluted with 170 ml of dry tetrahydrofuran and added slowly to a solution of 44.5 g of phthalic anhydride in 300 ml of tetrahydrofuran. After addition was complete, the resulting suspension was stirred at room temperature 1.5 hr, then heated under reflux 1 hr.

After cooling, most of the tetrahydrofuran was removed with a rotary evaporator. To the sticky, yellow residue was added 300 ml of cold water followed by enough concentrated hydrochloric acid to make the solution acidic. A yellow oily layer separated and was taken up by extraction with three portions of ether. The combined clear yellow ether layer was washed well with saturated sodium chloride solution, then extracted with three 120-ml portions of 10% sodium carbonate. The clear yellow combined aqueous extracts were boiled twice with charcoal and filtered (very little of the color was removed), cooled, and acidified with cold, concentrated hydrochloric acid. A light beige solid separated and was extracted with three 100-ml portions of ether. (A very intractable emulsion was encountered in these extractions.) The combined ether layers were filtered, washed with sodium chloride solution, and dried over sodium sulfate. After filtering, the ether was removed and the solid residue taken up in 200 ml of cold chloroform. Filtration removed a small amount of insoluble phthalic anhydride and evaporation of the chloroform gave 51.5 g of an ivory-colored solid, mp 122–130°.

This crude material was divided into four batches. Each batch was separately dissolved in the minimum amount of methylene chloride and pipetted onto a fresh 200 g column of silica gel wet packed in 2% methanol in methylene chloride. Elution with the same solvent mixture gave a combined total of 41.6 g (61.5%) of off-white material, mp 126–128°. Recrystallization from 40% benzene in cyclohexane yielded 37.6 g (55.5%) of 2-(2′-deuteriobenzoyl)benzoic acid as white platelets, mp 127.5–128.5°.

An analytical sample, mp 128–129°, was prepared by four recrystallizations from benzene–cyclohexane and sublimation at 100° (0.05 mm).

Anal. Calcd for $C_{14}H_9DO_3$: 10.00 atom % excess D. Found:[22] 9.50 atom % excess D.

2-Chloro-6-deuteriotoluene.—Freshly distilled 3-chloro-2-methylaniline was converted into 2-bromo-6-chlorotoluene by the procedure of Carpenter and Easter:[23] bp 68–69° (4 mm) [lit.[23] bp 60° (3 mm)], n^{20}D 1.5790 (lit.[23] n^{20}D 1.5791). The conversion of 2-bromo-6-chlorotoluene into 2-chloro-6-deuteriotoluene was carried out as described for the preparation of 2-deuteriochlorobenzene. The yield of material, bp 67° (35 mm), n^{20}D 1.5257, was 77%.

3-Deuterio-2-methylbenzhydrol.—The Grignard reagent was prepared from 5.15 g of magnesium and 27.0 g of 2-chloro-6-deuteriotoluene in 50 ml of dry tetrahydrofuran, initiated with a few drops of ethyl bromide and maintained at reflux for 1.5 hr. To the Grignard solution was added slowly 22.5 g of freshly distilled benzaldehyde in 35 ml of tetrahydrofuran.

After cooling, the suspension was hydrolyzed with 200 ml saturated ammonium chloride solution. Organic material which separated as a yellow upper layer was extracted with three portions of ether. The combined ether extracts were washed several times with brine and dried over sodium sulfate. Filtration followed by removal of ether with a rotary evaporator produced an oily yellow semisolid. Recrystallization of this material from 300 ml of petroleum ether (30–60°) gave 29.8 g (71%) of ivory-colored prisms, mp 90.0–92°. Further recrystallization including two treatments with Norit gave pure 3-deuterio-2-methylbenzhydrol as brittle clumps of white prisms, mp 90.5–92° (lit.[24] mp 90.5–91.0°).

The C–D band at 4.45 μ is clearly visible in the infrared spectrum of this material. In contrast, the spectrum of 2-methylbenzhydrol is completely free of absorption in this region. The two spectra also show subtle differences in the fingerprint region and in the intensity of the two strong bands at 6.7 and 6.9 μ.

2-Benzoyl-6-deuteriobenzoic Acid.—Chromium trioxide (40 g, 0.4 mol) was stirred into a mixture of 350 ml of glacial acetic acid, 10 ml of concentrated sulfuric acid and 100 ml of water. To this solution was added 11.92 g (60 mmol) of 3-deuterio-2-methylbenzhydrol in several portions. After the initial exothermic reaction subsided, the reaction mixture was heated under reflux 8.5 hr, cooled, and poured over 500 g of ice. Sodium bisulfite was added to destroy excess chromium trioxide. The solution was further diluted with 2 l. of cold water and extracted with two 500-ml portions of ether. The combined ether extracts were washed carefully with water to remove residual chromium salts. The concentrated ether extracts were extracted with 125 ml of 10% sodium bicarbonate and the basic solution was cooled and acidified with concentrated hydrochloric acid to give a white solid. One recrystallization from 30% benzene in cyclohexane yielded 6.4 g (47%) of white crystals of 2-benzoyl-6-deuteriobenzoic acid, mp 124.5–126.5°. An additional recrystallization provided material melting at 127–128.5°. The infrared spectrum of this material differed substantially from that of 2-(2′-deuteriobenzoyl)benzoic acid as well as from that of ordinary *o*-benzoylbenzoic acid.

1-Deuterioanthraquinone.—In a 100-ml flask was placed 2.5 g of 2-benzoyl-6-deuteriobenzoic acid and 20 ml of concentrated sulfuric acid. The resulting clear solution was protected with a calcium chloride drying tube and magnetically stirred while heated to 100° for 4 hr. The reaction mixture was then cooled and poured over 100 g of ice to give a woolly, voluminous tan solid. To coagulate the solid, this aqueous suspension was heated to boiling for a few minutes. After cooling, the solid was collected by suction filtration and washed well with several portions of hot water, then with dilute ammonium hydroxide, and again with hot water. The crude product was dried in the oven and recrystallized from toluene. A second recrystallization gave 2.05 g (90%) of 1-deuterioanthraquinone as long, silky needles, mp 284–286° (Kofler hot stage, corrected).

Three recrystallizations from toluene followed by drying (78° at 0.1 mm) and sublimation (135° at 0.05 mm) provided an analytical sample, mp 285–286° (hot stage).

(18) Melting points were determined in a Hershberg apparatus except as noted. Infrared spectra were taken using a Perkin-Elmer Model 137 Infracord.

(19) *o*-Bromochlorobenzene was purified by careful distillation through a 90-cm spinning-band column. A center cut boiling at 72° (9 mm) was collected. Vapor phase chromatography (silicon oil column at 142°) showed this material to be homogeneous except for a trace impurity which had the same retention time as *p*- or *m*-bromochlorobenzene. Authentic 1% solutions of these isomers in the distilled *o*-bromochlorobenzene were prepared and analyzed by vpc. Comparison of the relative peak heights with these chromatograms showed that the trace impurity present in *o*-bromochlorobenzene amounted to no more than 0.1%.

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Anal. Calcd for $C_{14}H_7DO_2$: 12.50 atom % excess D. Found: 12.30 atom % excess D (98.5%) (an independent mass spectral analysis gave a value of 98.4%).[25]

This experiment also serves to establish that deuterioanthraquinone is stable under the experimental conditions for its formation and does not suffer loss of deuterium.

Kinetic Procedures. General Method.—All kinetic runs were conducted in "twinned pairs" using 1-cm quartz cells mounted within the cell compartment of a Beckman DU spectrophotometer equipped with dual thermospacers. For any given run, solutions of 2-(2′-deuteriobenzoyl)benzoic acid and *o*-benzoylbenzoic acid in the appropriate sulfuric acid were prepared just before use (as described below). The acid used to make these solutions was always withdrawn by pipet from the same batch of sulfuric acid which had been previously standardized. Acid used for the reference cell was likewise removed from the same batch of sulfuric acid for any given run. All three cells were then placed in the Beckman compartment and allowed to equilibrate for 20–25 min. Changes in optical density due to absorption of the product anthraquinone were recorded in the usual fashion by taking readings at appropriate intervals, first of the 2-(2′-deuteriobenzoyl)benzoic acid solution and then of the *o*-benzoylbenzoic acid solution. The wavelength used varied in the range 269–281 mμ depending on the strength of the sulfuric acid solvent. Infinity points were taken after (at least) 10 half-lives.

Calculation of the Data.—Raw optical density data were converted into per cent unreacted and were plotted *vs.* time. The first-order plots remained linear to at least 90% reaction. Rate constants were obtained from slopes of lines in the usual fashion.

Preparation of Solutions.—Stock amounts of the kinetic acids were prepared by diluting 30% fuming sulfuric acid to the desired concentration with sulfuric acid. Ordinary reagent grade sulfuric acid was used without further purification. All kinetic acids were titrated in triplicate using approximately 1 *N* sodium hydroxide which had been freshly standardized against potassium acid phthalate.

Stock solutions of 2-(2′-deuteriobenzoyl)benzoic acid and *o*-benzoylbenzoic acid were prepared by weighing out approximately 1.7 mg of each material in 100-ml volumetric flasks. Filling to the mark with chloroform provided solutions close to 7.5×10^{-5} *M*. Just before a kinetic run, a 1-ml aliquot of each solution was withdrawn and pipetted into a separate 10-ml volumetric flask. The chloroform was then evaporated in a gentle stream of dry nitrogen, and both flasks were dried for a short time in the oven before being filled to the mark with stock sulfuric acid of the desired concentration. After being thoroughly shaken these sulfuric acid solutions were transferred to 1-cm cells by means of a pipet. The concentration of the solutions used for kinetic runs was thus approximately 7.5×10^{-6} *M*.

Analysis of Standard Mixtures.—Approximately 20 mg of pure anthraquinone and 40 mg of pure 1-deuterioanthraquinone were accurately weighed into a small flask. The mixture was dissolved in benzene to assure homogeneity. After evaporation of the benzene in a stream of dry nitrogen, the anthraquinone was sublimed to give a sample for mass spectral analysis. Mass spectra were obtained at low ionizing voltages (10–15 V)[25] and the parent peaks were used to calculate the percentage of 1-deuterioanthraquinone present. Table I presents results of five determinations.

TABLE I

ANALYSIS OF STANDARD MIXTURES OF ANTHRAQUINONES

% 1-deuterioanthraquinone by weight	62.9	60.6	63.6[a]
% 1-deuterioanthraquinone by mass spectra	63.0	61.2	64.2, 63.4, 64.1

[a] This sample was sublimed in three successive fractions and each analyzed.

Product Isolation.—Approximately 1 g of 2-(2′-deuteriobenzoyl)benzoic acid was weighed out into a 25-ml volumetric flask. The flask was filled with sulfuric acid of the appropriate concentration and placed in an oil bath at 70°. After a period of time corresponding to 10–12 half-lives, the flask was removed from the bath and cooled, and the contents were poured over ice. The precipitate was filtered and washed thoroughly with water, a small amount of ammonia, and then again with water. The dried anthraquinone was crystallized from toluene, and sublimed to give a sample for mass spectral analysis.

A further control experiment in which a sample of 1-deuterioanthraquinone was heated with fuming sulfuric acid showed no loss of deuterium.

(25) The mass spectra were determined with a CEC Model 21-103 C mass spectrometer equipped with an ion multiplier. We thank Miss S. Firth for obtaining the mass spectra.

Results and Discussion

Kinetic Measurements.—The results of a series of kinetic measurements are presented in Table II. Above 100% sulfuric acid, the kinetic isotope effect k_H/k_D remains nearly constant. Below 100% sulfuric acid the value for k_H/k_D gradually increases. However, concurrently the rate of formation of anthraquinone remains nearly constant from 97 to 100% sulfuric acid, and is somewhat higher in fuming sulfuric acid. In 97% sulfuric acid (at 70°) *o*-benzoylbenzoic acid is substantially, but not entirely, converted into the lactol carbonium ion. It, therefore, appears that the kinetic isotope effects below 100% sulfuric acid are mediated by a secondary isotope effect on the equilibrium formation of the lactol carbonium ion.

TABLE II

RATE OF CYCLIZATION OF *o*-BENZOYLBENZOIC ACID AND 2-(2-DEUTERIOBENZOYL)BENZOIC ACID AT 70.0°

Run	Wt % H_2SO_4	$10^4k_{obsd}^H$, sec^{-1}	$10^4k_{obsd}^D$, sec^{-1}	k_H/k_D	Average k_H/k_D
1	97.13	1.27	0.987	1.29	
2	97.13	1.28	0.998	1.28	1.28 ± 0.02
3	97.13	1.26	0.998	1.26	
4	98.18	1.46	1.20	1.22	1.22
5	98.18	1.45	1.20	1.21	
6	99.23	1.56	1.35	1.16	1.16
7	99.23	1.56	1.34	1.16	
8	100.3	1.53	1.39	1.10	
9	100.3	1.56	1.38	1.13	1.13 ± 0.03
10	100.3	1.61	1.39	1.16	
11	101.3	1.98	1.66	1.19	1.19 ± 0.01
12	101.3	1.97	1.67	1.18	
13	101.3	1.97	1.65	1.19	
14	102.1	2.39	2.03	1.18	1.18
15	102.9	2.98	2.45	1.22	
16	102.9	2.85	2.40	1.19	1.20 ± 0.02
17	102.9	2.90	2.41	1.20	

Product Isolation.—Cyclization of 2-(2′-deuteriobenzoyl)benzoic acid gives a mixture of anthraquinone and 1-deuterioanthraquinone. The percentage of 1-deuterioanthraquinone formed in eight different sulfuric acid media is given in Table III.

TABLE III

PERCENTAGE OF 1-DEUTERIOANTHRAQUINONE IN ANTHRAQUINONE PRODUCT MIXTURES

Wt % H_2SO_4	% 1-Deuterioanthraquinone
97.13	56.6
98.18	57.5
99.23	58.3
100.3	59.2
101.3	60.0
102.1	60.7
102.9	61.2
104.9	62.6

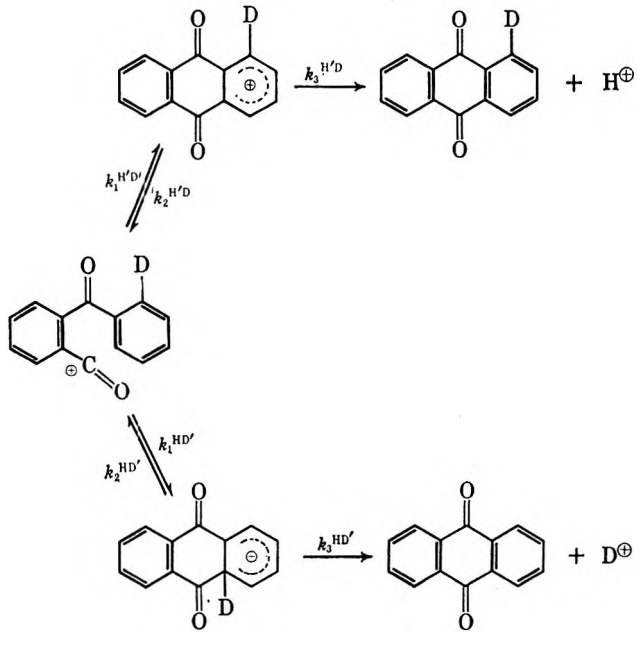
It is to be noted that the fraction of deuterium retained increases smoothly from 97% sulfuric acid to 105% sulfuric acid. This is in contrast to the behavior of the measured kinetic isotope effects discussed above.

In evaluating the significance of these results it is worthwhile to consider first the possibility that formation of the Wheland intermediate is rate limiting and followed by a fast collapse to products. This picture of the reaction sequence is inconsistent with the generally accepted conclusion that there is not a substantial isotope effect in the formation of the Wheland intermediate. Were this picture correct the ratio ($k_1^{H'D}/k_1^{HD'}$) (H'D superscript signifies attack at the hydrogen site; HD' superscript signifies attack at the deuterium site) would have to vary from 1.3 to 1.6, very much larger than any previously observed secondary isotope effects in the aromatic substitution process.

Thus, we conclude that these kinetic and product isotope effects demonstrate that decomposition of the Wheland intermediate is partially rate limiting. Denney and Klemchuk[16] have concluded that this same situation obtains in the formation of fluorenone from *o*-phenylbenzoic acid.

Consider the situation summarized in Chart I.

CHART I



The rate of formation of deuterated anthraquinone from 2-(2'-deuteriobenzoyl) acid may be directly obtained by making use of the knowledge of the fraction of deuterium retained in the product anthraquinone. Correcting the observed total rate of formation of anthraquinone in this fashion leads to the results tabulated in column 2 of Table IV. This rate is given by eq 1 in which it is to be noted that the rate constants

$$k_{obsd}^{H'D} = k_1^{H'D}k_3^{H'D}/(k_2^{H'D} + k_3^{H'D}) \quad (1)$$

involve only indirect and secondary isotope effects. This rate of reaction may further be compared with the rate of formation of ordinary anthraquinone from benzoylbenzoic acid (statistically corrected by factor of 2) with the results given in column 4 of Table IV. It

TABLE IV

DERIVED ISOTOPE EFFECTS

Wt % H_2SO_4	[a], $10^4 \frac{k_1^{H'D}k_3^{H'D}}{k_2^{H'D} + k_3^{H'D}}$, sec^{-1}	[b], $10^4 \frac{k_1^{HD'}k_3^{HD'}}{k_2^{HD'} + k_3^{HD'}}$, sec^{-1}	[c] $\frac{1/2k^{HH}}{k^{H'D}}$	[c] $\frac{1/2k^{HH}}{k^{HD'}}$
97.13	0.56	0.43	1.13	1.48
98.18	0.69	0.51	1.06	1.43
99.23	0.78	0.56	0.994	1.39
100.3	0.82	0.57	0.957	1.39
101.3	1.00	0.66	0.990	1.48
102.1	1.23	0.80	0.971	1.50
102.9	1.48	0.90	0.980	1.55

[a] Rate of formation of deuterioanthraquinone. [b] Rate of formation of ordinary anthraquinone. [c] Average in region 99–103% H_2SO_4, 0.978 ± 0.01.

is to be noted that the resulting isotope effect is very small and slightly inverse; in the region between 99 and 103% sulfuric acid, k_H/k_D is 0.978 ± 0.01.

Similarly, the fraction of ordinary anthraquinone obtained from 2-(2'-deuteriobenzoyl)benzoic acid allows calculation of the rate of reaction at the deuterium site (column 3, Table IV.) This rate (eq 2) now represents

$$k_{obsd}^{HD'} = k_1^{HD'}k_3^{HD'}/(k_2^{HD'} + k_3^{HD'}) \quad (2)$$

a combination of secondary isotope effects ($k_1^{HD'}$ and $k_2^{HD'}$) in the formation of the Wheland intermediate and its reversion to its precursor. In addition the important primary isotope effect involved in the decomposition of the Wheland intermediate to products ($k_3^{HD'}$) is encompassed in the rates given in column 3 of Table IV. The isotope effect involved is calculated in column 5 in Table V, and is 1.46 ± 0.05.

Thus, the secondary isotope effects are negligible; a primary isotope effect is operative, and hence, the decomposition of the Wheland intermediate is partially rate limiting.

Registry No.—Anthraquinone, 84-65-1; 2-(2'-deuteriobenzoyl)benzoic acid, 15733-67-2; 2-chloro-6-deuteriotoluene, 15733-68-3; 2-benzoyl-6-deuteriobenzoic acid, 15733-69-4; 1-deuterioanthraquinone, 7302-30-9; *o*-benzoylbenzoic acid, 85-52-9.

Transmission of Substituent Effects in Quinoline

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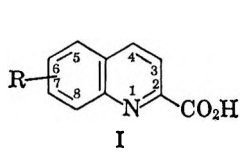
Dissociation constants of quinoline-2-carboxylic acids (25°), in 44.25% (w/w) aqueous ethanol, were found to satisfy the Hammett equation. These acids gave a ρ value of 1.782 with $s = 0.063$ and $r = 0.996$.

Whereas several workers have studied the effect of substituents on the basicity of the nitrogen in quinoline,[2,3] very little work has been reported on the transmission of substituent effects to other reaction sites in the quinoline nucleus. One such study was conducted by Illuminati, who, along with several coworkers,[3,4] investigated the rates of methoxy dechlorination of 2- and 4-chloroquinolines with substituents in various positions both in the heterocyclic ring and in the carbocyclic ring. Since this reaction involves nucleophilic attack directly on the ring, the Hammett substituent constants are σ^- values.

In order to evaluate the applicability of the Hammett equation to the transmission of substituent effects in quinoline using a reaction where normal σ values could be employed, we examined a series of substituted quinolinecarboxylic acids. Two sets of acids were studied, quinoline-2-carboxylic acids (I) substituted in the 4, 6, and 8 positions and quinoline-4-carboxylic acids (II) substituted in the 2 position.



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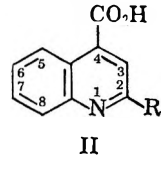

II

Results and Discussion

pK_a Values.—These values were determined by potentiometric titration. The solvent employed was 44.25% (w/w) aqueous ethanol. The values obtained are given in Table I. Corrections were made for the medium effect and the residual liquid-junction error.[5]

Data Used in Correlations.—A comprehensive theory for calculating substituent constants in aromatic systems was suggested by Dewar and Grisdale.[6] According to this theory, the σ constant for a substituent at position i when the reaction site is at position j is given by eq 1 where r_{ij} is the distance (in benzene C–C

$$\sigma_{ij} = F/r_{ij} + Mq_{ij} \quad (1)$$

bond lengths) between positions i and j, and q_{ij} is the formal charge at position j produced by attaching the $-CH_2^-$ group at position i. F is a measure of the field effect caused by the electric dipole of the substituent–substrate bond, and M is a measure of the π-inductive resonance effect of the substituent. F and M, and ultimately, therefore, σ_{ij}, can be expressed in terms of σ_m and σ_p from the benzene series. This is convenient because there are well-established values of σ_m and σ_p.[7] The appropriate relationships for two fused six-membered rings were derived by Barlin and Perrin,[8] and it was these relationships, along with the σ_m and σ_p values of McDaniel and Brown, which we used to calculate substituent constants for use in our correlations. McDaniel and Brown do not give a σ_m value for the aza group; so the value used was that of Barlin and Perrin.[9] Table II gives the σ constants which we employed in our correlation studies.

TABLE I

pK_a VALUES OF QUINOLINECARBOXYLIC ACIDS IN 44.25% (W/W) AQUEOUS ETHANOL AT 25 ± 0.1°

Acid	No.	pK_a	n[a]	Av dev[b]
Quinoline-2-carboxylic	1	4.95	5	2.8
4-Aza	2	3.69	4	4.7
4-Chloro	3	4.28	5	3.7
4-Methoxy	4	6.29	4	2.4
6-Methyl	5	5.14	4	0.5
8-Nitro	6	4.15	4	2.4
Quinoline-3-carboxylic	7	4.59	4	1.1
Quinoline-4-carboxylic	8	4.42	5	3.2
2-Bromo	9	3.38	5	3.6
2-Chloro	10	3.37	7	11.9
2-Hydroxy	11	3.46	5	9.3

[a] Number of determinations. [b] In parts per thousand.

Correlations.—The unmodified Hammett equation was applied to these two sets of acids (see eq 2). The

$$pK = -\rho\sigma + pK^\circ \quad (2)$$

reaction constant (ρ), the standard deviation (s), the correlation coefficient (r), and the regression intercept (pK° calcd) were calculated using the formulae given by Jaffé.[10] We applied eq 2 to the data for 4-aza-, 4-chloro-, 6-methyl-, 8-nitro-, and unsubstituted quinoline-2-carboxylic acids and found $\rho = 1.782$, $s = 0.063$, and $r = 0.996$. Thus, the confidence level is greater than 99%.

The regression intercept (pK° calcd) was 5.00. This compares favorably with the observed value of 4.95 for the pK_a of quinoline-2-carboxylic acid.

The data for 4-methoxyquinoline-2-carboxylic acid were not included in the correlation because the pK_a for this acid was much higher than expected. The methoxy group has a positive σ_m value (electron withdrawing) and so this acid would be expected to be stronger than the unsubstituted acid. On the other

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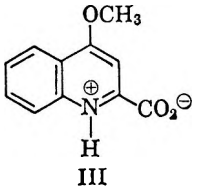
TABLE II

SUBSTITUENT CONSTANTS USED IN CORRELATIONS

Substituent	COOH position	j[a]	a	Relationship for calculating σ_{ij}[b]	σ_m[c]	σ_p[c]	σ_{ij}
H	2 or 4				0.00	0.00	0.00
4-Aza	2	2	4	σ_m	0.73		0.73
4-Chloro	2	2	4	σ_m	0.373		0.373
4-Methoxy	2	2	4	σ_m	0.115		0.115
6-Methyl	2	2	6	0.58 σ_m	−0.069		−0.040
8-Nitro	2	2	8	0.35 σ_m + 0.35 σ_p	0.710	0.778	0.521
2-Bromo	4	1	3	σ_m	0.391		0.391
2-Chloro	4	1	3	σ_m	0.373		0.373
2-Hydroxy	4	1	3	σ_m	0.121		0.121

[a] In order to use the available relationships for calculating σ_{ij}, the reaction center (j) has been designated the 1 position or the 2 position. Thus, the carboxyl group in quinoline-4-carboxylic acids is said to be at the 1 position, and the position of a substituent (i) is designated accordingly. [b] Reference 8. [c] Reference 7, except for the value of σ_m for the aza group which is from ref 9.

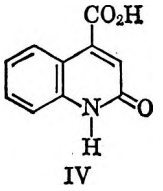
hand, its σ_p value is negative (electron donating). When its σ_{ij} value is calculated for transmission from the 4 position to the heteroatom in quinoline, it is found to be −0.415, indicating a very strong electron donor. It is possible, therefore, that the 4-methoxy group increases the basicity of the nitrogen to such an extent that the acid exists in the zwitterionic form (III), and



III

the pK_a value determined in our study would represent loss of a proton from nitrogen rather than from the carboxyl group. This conclusion is confirmed by the fact that, when the infrared spectra of all the acids were studied in the solid state in KBr, only this acid did not show an absorption band in the 1725–1680-cm^{-1} region. Further evidence for form III may be obtained by comparing the pK_a of the acid with that of 4-methoxyquinoline which is reported to be 6.65, in water, at 25°.[11] This compares well with the value obtained for the acid (6.29) since the electron-withdrawing 2-carboxylate group would be expected to lower the pK_a. When the data for 4-methoxyquinoline-2-carboxylic acid were included in the correlation, it was found that ρ = 2.308, s = 0.656, and r = 0.772. These values indicate a poor correlation.

The data for quinoline-4-carboxylic acids were insufficient for a statistical study. The pK_a of 2-hydroxyquinoline-4-carboxylic acid was not included in the correlation because of the probability that this acid exists in the keto form (IV). Evidence that this is the



IV

case is provided by the infrared spectrum of the solid acid in KBr. The spectrum has a very strong amide band at 1658 cm^{-1}. Only three acids were available, therefore, in the quinoline-4-carboxylic acid series. Two of these had closely related chloro and bromo groups, and a statistical study of these data would not have much meaning. A reaction constant was calculated, however, by substituting the appropriate data for 2-bromoquinoline-4-carboxylic acid in eq 2. By this means, it was found that ρ = 2.7. More data are necessary before an adequate conclusion can be drawn.

Tautomerism.—It is recognized that there is a possibility that all of these acids can exist to some extent in zwitterionic forms such as III. Two groups of workers have examined the problems involved in applying the Hammett equation to tautomeric systems.[12,13] Kabachnik[13] showed that the dissociation constants of tautomeric acids follow the Hammett equation only when the tautomeric equilibrium is strongly shifted toward one of the forms. Our results indicate that this equilibrium is shifted toward the neutral form. As a further test of the predominance of this form, a correlation study was attempted using our pK_a values for the set of 2-acids, and substituent constants for transmission to the 1 position rather than the 2 position of the quinoline ring. It was found that ρ = 1.742, s = 0.371, and r = 0.933. Thus, the correlation is poor, confirming our conclusion concerning the neutral nature of the acids.

The values of ρ for 4-substituted quinolines in 50% aqueous ethanol and in water were reported to be 6.15 and 5.72, respectively.[14] In the quinoline-2-carboxylic acids, if ionization were occurring at the nitrogen atom, the value of ρ should be comparable with the values obtained for the 4-substituted quinolines. The fact that ρ is much lower (1.7) indicates that this is not the reaction which is taking place.[15]

Experimental Section

Preparation of Acids.—Quinoline-2-carboxylic acid, quinoline-4-carboxylic acid, and 2-hydroxyquinoline-4-carboxylic acid were obtained from commercial sources, recrystallized to constant melting point, dried under reduced pressure, and analyzed. All the other acids were prepared according to reported methods and similarly purified and analyzed. 4-Azaquinoline-2-carboxylic acid (quinoxaline-2-carboxylic acid) was prepared by the method of Maurer and Boettger,[16] 4-chloroquinoline-2-carboxylic acid by the method of Spath,[17] and 8-nitroquinoline-2-carboxylic

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(15) We thank the referee for this suggestion.

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(17) E. Spath, *Monatsch. Chem.*, **42**, 89 (1921).

acid by the method of Roth and Erlenmeyer.[18] 6-Methylquinoline-2-carboxylic acid[19] was prepared by a method similar to that described by Kaslow and Stayner[20] for the synthesis of 4-methylquinoline-2-carboxylic acid. 4-Methoxyquinoline-2-carboxylic acid[21] was prepared by the methylation of kynurenic acid with diazomethane. 2-Bromoquinoline-4-carboxylic acid[22] and 2-chloroquinoline-4-carboxylic acid[23] were prepared by the action of phosphorus halides on the 2-hydroxy acid.

pK_a Values.—The pK_a values were determined by potentiometric titration. pH Values were measured between 30 and 70% neutralization using a Beckman Expandomatic pH meter. The electrodes were standardized before each determination in aqueous buffers, and the standardization was checked following completion of the titration. A correction was applied to the pH values for the medium effect and the residual liquid-junction error. The value for this correction (0.18 pH unit) was obtained for 44.25% ethanol by interpolation using values given by Bates[5] for other aqueous ethanol solvents. A correction was also made for hydrogen ion activity. The temperature of the solutions was maintained at 25.0 + 0.1° by measuring the pH of the solutions in a jacketed beaker through which was pumped water from a constant-temperature bath. The average of values for six to nine points in one titration constituted one determination.

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Registry No.—1, 93-10-7; 2, 879-65-2; 3, 15733-82-1; 4, 15733-83-2; 5, 15733-84-3; 6, 15733-85-4; 7, 6480-68-8; 8, 486-74-8; 9, 15733-87-6; 10, 5467-57-2; 11, 15733-89-8; quinoline, 91-22-5.

Acknowledgments.—We wish to thank Miss Susan Tatelbaum for the preparation of 8-nitroquinoline-2-carboxylic acid. Appreciation is expressed to the University of Pennsylvania and to the National Science Foundation for financial assistance to Charles W. Donaldson.

The Reactions of β-Dicarbonyl Compounds with Tetrakis(dimethylamino)titanium

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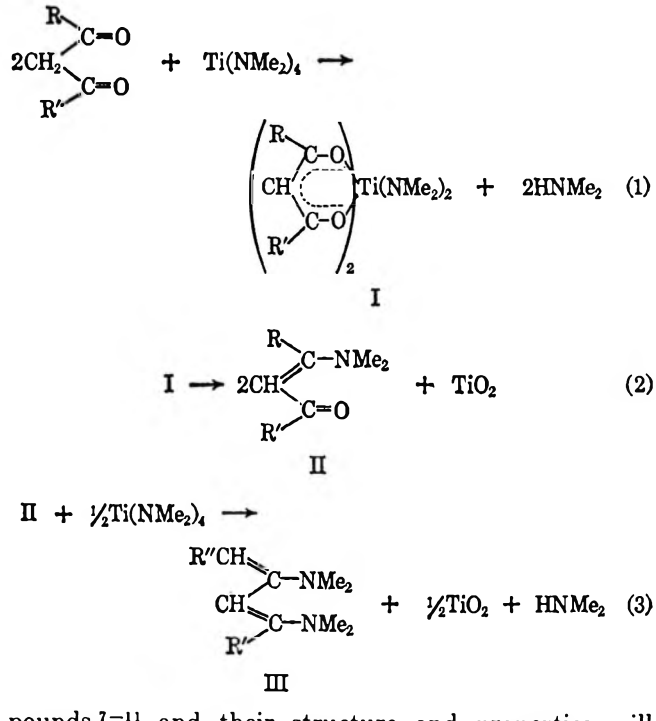
β-Dicarbonyl compounds ($RCOCH_2COR'$) have been found to react with tetrakis(dimethylamino)titanium to give complexes, enamine amides, enamine esters, ketenamines, and the previously unknown dienediamines and dienetriamines depending on the nature of the R and R′ groups.

The amination of carbonyl containing organic compounds by $B(NR_2)_3$, $P(NR_2)_3$, $As(NR_2)_3$, and $Ti(NR_2)_4$ has recently been the subject of several papers.[1-6] In the reactions with aldehydes, ketones, and carboxylic acids, the relative order of reactivity has been found to be $Ti(NR_2)_4 \gg As(NR_2)_3 > P(NR_2)_3$. $B(NR_2)_3$ and $P(NR_2)_3$ react with β-diketones and β-keto esters yielding enamino ketones and β-enamino esters or amides, respectively.[1,6] This paper presents the results of a study of the reactions of the much more reactive $Ti(NR_2)_4$ with some representative β-diamides, β-diesters, β-ketamides, β-keto esters, and β-diketones.

Results and Discussion

Tetrakis(dimethylamino)titanium reacts with β-dicarbonyl compounds according to eq 1, 2, and 3, where the nature of the products obtained depends upon the substituents R and R′ and the ratio of $Ti(NMe_2)_4$ to carbonyl compound. Reactions of all other aminating agents studied with β-dicarbonyl compounds stop at the enamine (II). However, with $Ti(NMe_2)_4$, two new classes of compounds, 1,3-diene-1,3-diamines (III) and 1,3-diene-1,1,3-triamines (III, R′ = NMe_2), can be formed.

N,N,N′,N′-Tetramethylmalonamide and dimethyl malonate both react with $Ti(NMe_2)_4$ to yield deep red complexes (I, R = R′ = NMe_2 and R = R′ = OMe, respectively). These complexes are analogous to the dihalo- and dialkoxybis(β-diketonato)titanium compounds,[7-11] and their structure and properties will presently be the subject of another paper.



Methyl acetoacetate and N,N-dimethylacetoacetamide react with $Ti[N(CH_3)_2]_4$ to yield methyl 3-(dimethylamino)crotonate (II, R = CH_3 and R′ = OCH_3)[12] and 3-(dimethylamino)-N,N-dimethylcroton-

(1) P. Nelson and A. Pelter, *J. Chem. Soc.*, 5142 (1965).
(2) H. Weingarten and W. A. White, *J. Amer. Chem. Soc.*, **88**, 850 (1966).
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(10) M. Cox, R. J. H. Clark, and H. J. Milledge, *Nature*, **212**, 1357 (1966).
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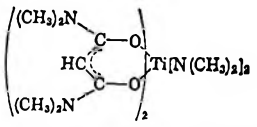
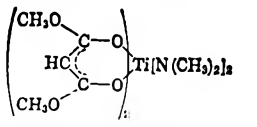
(12) *Cf.* the reactions of $P(NR_2)_3$ and $B(NR_2)_3$ with β-keto esters given in ref 1 and 6.

TABLE I

Compound (no.)	Yield,[a] %	Anal., % Calcd C	H	N	Ti	Found C	H	N	Ti	Mol wt[b]	Bp (mm), °C	$n^{25}D$	Nmr[c] (τ)	Ir, cm^{-1}[d] $\gamma_{C=O}$	$\gamma_{C=C}$
 Bis(dimethylamino)bis(dimethylmalonato)titanium (1)	75	42.2	6.5	7.0	12.1	42.4	6.8	7.3	12.0	398 ± 1	87–89 (mp)		(s) 5.39, 6.40, 6.61 (bd)[d,e] (1:6:6)	1643	1614
 Bis(dimethylamino)bis(N,N,N′,N′-tetramethylmalonamidato)titanium (2)	84	48.0	8.4	18.7	10.7	47.5	8.4	18.7	10.5	458 ± 10[f]	119–120 (mp)		(s) 5.74, 6.30 (bd), 7.30 (1:6:12)	1574	1539
$CH_2=C(N(CH_3)_2)-CH=CH-CO_2CH_3$ Methyl 3-(dimethylamino)crotonate (3)	50	58.7	9.1	9.8		58.4	9.0	10.0		143	50 (0.15)	1.5250	(s) 5.06 (bd), 6.23, 7.55, 7.70 (1:3:3:6)	1694	1590
$CH_2=C(N(CH_3)_2)-CH=CH-CON(CH_3)_2$ 3-(Dimethylamino)-N,N-dimethylcrotonamide (4)	51	61.5	10.2	18.4		61.9	9.9	18.1		156	94 (0.4)	1.5451	(s) 5.29, 7.18, 7.54, 7.57 (1:6:3:6)	1617	1577
$CH_2=C(N(CH_3)_2)-CH=C(N(CH_3)_2)-N(CH_3)_2$ N,N,N′,N′N″,N″-Hexamethyl-1,1,3-butadienetriamine (5)	77	65.6	11.5	22.9		65.1	11.8	22.9		183	43 (0.4)	1.5129	(d) 5.88, 6.02; (m) 6.27; (s) 7.37, 7.41, 7.54 (1:1:1:6:6:6)		1620
$(CH_3)_3C-C(N(CH_3)_2)=CH-COC(CH_3)_3$ 3-(Dimethylamino)-2,2,6,6-tetramethyl-3-hepten-5-one (6)	64	74.0	11.8	6.6		74.3	11.3	6.6		211	49 (0.2)	1.4917	(s) 4.31, 7.33, 8.76, 8.90 (1:6:9:9)	1645	1544
$CF_3-C(N(CH_3)_2)=CH-COCF_3$ 2-(Dimethylamino)-1,1,1,5,5,5-hexafluoro-2-penten-4-one (7)	75	35.7	3.0	6.0		35.4	3.1	6.4		235	48 (4)	1.4212	^1H (q) 4.22, J_{FH} = 0.5 cps, 7.57, J_{FH} = 0.8 cps (1:6) ^{19}F (heptet) 66.1 ppm, J_{FH} = 1.0 cps; (s) 77.6 ppm (1:1)[g]	1674	1588
$CH_2=C(N(CH_3)_2)-CH=C(N(CH_3)_2)-CH_3$ N,N,N′N′-Tetramethyl-1,3-pentadiene-2,4-diamine (8)	70	70.1	11.7	18.2		69.9	11.4	18.2		154	55 (1.2)	1.5108	(s) 5.46 (bd); 6.28 (bd); (m) 6.42; (s) 7.40, 7.46; (d) 8.90 (1:1:1:6:6:3)[g]		1630
$CH_2=C(N(CH_3)_2)-CH=C(N(CH_3)_2)-C_6H_5$ N,N,N′,N′-Tetramethyl-1-phenyl-1,3-butadiene-1,3-diamine (9)	70	77.8	9.2	13.0		77.4	9.2	13.0		216	82 (0.3)	1.5653	(m) 2.36, 3.00; (m) 4.92, 6.20; (d) 6.23; (s) 7.48, 7.63 (5:1:1:1:6:6) (m) 2.36, 3.00; (d) 4.82; (s,bd) 5.90; (?)[h] 6.17; (s) 7.41, 7.47 (?)[i] (5:1:1:1:6:6)[j,k]		1615

[a] No special effort was made to optimize yields. [b] Molecular weights were determined by mass spectroscopy. [c] Benzene solvent, TMS internal standard except where otherwise stated. [d] PhCN solvent. In benzene solution the OMe and NMe_2 adsorption have approximately the same chemical shifts. [e] bd, unusually broad peak. [f] $CFCl_3$ as external standard. [g] Neat material. [h] Multiplicity uncertain. [i] Position uncertain. [j] Two isomers present in 4:1 ratio. [k] C_6D_6 solvent. [l] Cryoscopy in benzene.

amide (II, R = CH_3 and R′ = NMe_2), respectively. Reaction of the crotonamide with excess $Ti[N(CH_3)_2]_4$ gives N,N,N′,N′,N″,N″-hexamethyl-1,1,3-butadienetriamine (III, R′ = NMe_2 and R″ = H). The same product is obtained from methyl 3-(dimethylamino)-crotonate, the reaction proceeding stepwise *via* the amide.

β-diketones which have no hydrogens on the α-carbon of the R or R′ groups react with $Ti[N(CH_3)_2]_4$ to give enamino ketones. For example, dipivaloylmethane and hexafluoroacetylacetone react to form 3-(dimethylamino)-2,2,6,6-tetramethyl-3-hepten-5-one (II, R = R′ = *t*-butyl) and 2-(dimethylamino)-1,1,1,5,5,5-hexafluoro-2-penten-4-one (II, R = R′ = CF_3), respectively.

However, β-diketones with hydrogens on the α-carbon atom of either the R or R′ groups react vigorously with $Ti[N(CH_3)_2]_4$ to give the previously unknown 1,3-diene-1,3-diamines in good yield. Acetylacetone and benzoylacetone form N,N,N′,N′-tetramethyl-1,3-pentadiene-2,4-diamine[13] (II, R″ = H and R′ = CH_3) and N,N,-N′,N′-tetramethyl-1-phenyl-1,3-butadiene-1,3-diamine (III, R″ = H and R′ = C_6H_5), respectively. Similar reactions were found to take place, on the nmr scale, with dimedone and 1-acetylcyclohexanone.

The physical and analytical properties of the compounds prepared are collected in Table I and are all consistent with the assigned structures. The $\gamma_{C=O}$ and $\gamma_{C=C}$ bands for the complexes were assigned after Behnke and Nakamoto.[14]

Addition of $Ti[N(CH_3)_2]_4$ to the β-dicarbonyl compounds always gave an intense red coloration indicating chelate formation which has been proposed as the first step in this type of reaction.[1] This color faded rapidly for the reactions of the titanium amide with methyl

(13) The reaction of tetrakis(dimethylamino)titanium with ferric acetyl acetonate was also found to give N,N,N′,N′-tetramethyl-1,3-pentadiene-2,4-diamine.

(14) G. T. Behnke and K. Nakamoto, *Inorg. Chem.*, **6**, 433 (1967).

acetoacetate, hexafluoroacetylacetone, and the β-diketones with hydrogen on the α-carbon of the R or R′ groups,[15] all of which reacted rapidly at ambient temperatures. However, for the other reactions which required heating under reflux for various lengths of time, the color persisted until the reaction neared its completion. Furthermore, for the slowest reaction, dipivaloylmethane with $Ti[N(CH_3)_2]_4$, the nmr spectrum showed a singlet at τ 4.0 and two multiplets in the *t*-butyl region, as expected for a β-diketone titanium complex,[7-11] which slowly decreased in intensity as the spectra of the product grew. Thus, the decomposition of the β-dicarbonyl–titanium complex is probably the rate-determining step of the reaction. The mechanism proposed is analogous to that outlined elsewhere[1,4] and will not be discussed further here.

In only one example studied was evidence for the formation of more than one geometric isomer obtained. The nmr spectrum of N,N,N′,N′-tetramethyl-1-phenyl-1,3-butadiene-1,3-diamine, as given in Table I, showed the presence of two isomers in the ratio 4:1. Certain of the peaks for the isomers present in low concentration were partially hidden leading to uncertainties in the multiplicity of one of the peaks and the chemical shift of another. The isomers are apparently present in their thermodynamic equilibrium concentrations since addition of a trace of acetic acid led to coalescence of the separate spectra into one set of broadened peaks and addition of strong base, $Ti[N(CH_3)_2]_4$, regenerated the original spectra with no change in relative concentration.

Experimental Section

Synthesis.—All the compounds were synthesized in an atmosphere of dry nitrogen. Analyses for C, H, N, and Ti were performed in the Physical Sciences Center, Central Research Department, Monsanto Co.

Bis(dimethylamino)bis(dimethylmalonato)titanium.—A solution of tetrakis(dimethylamino)titanium (2.24 g, 0.01 mol) in 20 ml of ether was added slowly, with stirring, to a solution of dimethyl malonate (2.64 g, 0.02 mol) in 20 ml of ether. After removal of the solvent deep red crystals were obtained which were recrystallized from pentane.

Bis(dimethylamino)bis(N,N,N′,N′-tetramethylmalonamidato)titanium.—A solution of tetrakis(dimethylamino)titanium (2.24 g, 0.01 mol) in 20 ml of ether was slowly added, with stirring, to a mixture of N,N,N′,N′-tetramethylmalonamide (3.16 g, 0.02 mol) in 20 ml of ether. After removal of the solvent, deep red crystals were obtained which were recrystallized from pentane.

Methyl 3-(Dimethylamino)crotonate.—A solution of tetrakis(dimethylamino)titanium (1.12 g, 0.005 mol) in 10 ml of ether was added dropwise, with vigorous stirring, to a solution of methyl acetoacetate (1.16 g, 0.01 mol) in 10 ml of ether. On addition of the titanium compound a deep red coloration was obtained which rapidly disappeared on stirring to leave an orange solution. After the addition was complete, stirring was continued for 2 hr and the reaction mixture was then left standing overnight. The titanium dioxide, which slowly separated out, was filtered off and the solvent was removed. Distillation of the remaining oil gave the colorless product.

3-(Dimethylamino)-N,N-dimethylcrotonamide.—A solution of tetrakis(dimethylamino)titanium (1.57 g, 0.007 mol) in 10 ml of ether was slowly added, with stirring, to a solution of N,N-dimethylacetoacetamide (1.61 g, 0.0125 mol) in 10 ml of ether and the resulting deep red solution was heated under reflux for 48 hr. The solvent was then removed and distillation of the remaining oil gave the pale yellow product. A small amount (10%) of N,N,N′,N′,N″,N″-hexamethyl-1,1,3-butadienetriamine was also isolated as a distillation forerun.

N,N,N′,N′,N″,N″-Hexamethyl-1,1,3-butadienetriamine.—A solution of tetrakis(dimethylamino)titanium (0.9 g, 0.004 mol) in 10 ml of ether was slowly added to a solution of 3-(dimethylamino)-N,N-dimethylcrotonamide (1.17 g, 0.0075 mol) in 10 ml of ether and the resulting deep red solution was heated under reflux for 96 hr. The solvent was then removed and distillation of the residue gave the colorless product.

3-(Dimethylamino)-2,2,6,6-tetramethyl-3-hepten-5-one.—A solution of tetrakis(dimethylamino)titanium (1.34 g, 0.006 mol) in 10 ml of ether was slowly added, with stirring, to a solution of dipivaloylmethane (1.84 g, 0.01 mol) in 10 ml of ether and the resulting deep red solution was heated under reflux for 5 days. The solvent was removed and distillation of the residue gave the pale yellow product.

2-(Dimethylamino)-1,1,1,5,5,5-hexafluoro-2-penten-4-one.—A solution of tetrakis(dimethylamino)titanium (1.2 g, 0.0054 mol) in 10 ml of ether was slowly added, with stirring, to a solution of hexafluoroacetylacetone (2.08 g, 0.01 mol) in 10 ml of ether and the resulting orange-red solution was left standing overnight. The white precipitate which formed was filtered off, the solvent was removed, and the residual oil was distilled to give the pale yellow product.

N,N,N′,N′-Tetramethyl-1,3-pentadiene-2,4-diamine.—A solution of tetrakis(dimethylamino)titanium (1.5 g, 0.0067 mol) in 10 ml of ether was slowly added, with stirring, to a solution of acetylacetone (0.6 g, 0.006 mol) in 10 ml of ether and the resulting deep red solution[15] was left standing for 12 hr. The precipitate of titanium dioxide, which slowly formed, was filtered off and the solvent was removed. Distillation of the remaining oil gave the colorless product.

N,N,N′,N′-Tetramethyl-1-phenyl-1,3-butadiene-1,3-diamine.—A solution of tetrakis(dimethylamino)titanium (1.2 g, 0.0053 mol) in 10 ml of ether was slowly added, with stirring, to a solution of 1-benzoylacetone (0.81 g, 0.005 mol) in 10 ml of ether and the resulting deep red solution[15] was left standing for 12 hr. The precipitate of titanium oxide, which slowly formed, was filtered off and the solvent was removed. Distillation of the remaining oil gave the colorless product.

Infrared Spectra.—A Beckman IR-4 was used and the spectra of the liquids were obtained using thin films and sodium chloride windows. The spectra of the complexes were obtained from Nujol mulls.

Nuclear Magnetic Resonance Spectra.—A Varian A-60 spectrometer was used for the nmr measurements. Chemical shifts are believed to be accurate to ±0.02 ppm and the coupling constants to ±0.2 cps. The ^{19}F magnetic resonance measurements were performed on a Varian A-56/60. Chemical shifts are believed to be accurate to ±0.1 ppm and coupling constants to ±0.2 cps.

Registry No.—1, 12239-98-4; 2, 12239-99-5; 3, 15895-69-9; 4, 15895-70-2; 5, 15895-71-3; 6, 15895-75-7; 7, 15895-72-4; 8, 15895-73-5; 9, 15895-74-6.

(15) Although the initial deep red color was rapidly lost after the initial addition of β-diketone, the solution slowly darkened as the addition was continued, presumably owing to the formation of side products containing large chromophores.

Chemistry of Tritylllithium. Condensation with Benzophenone in Tetrahydropyran

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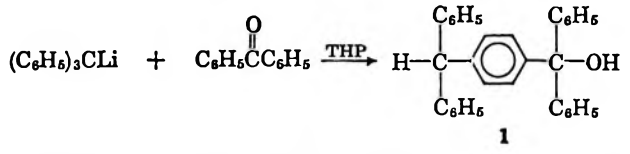
Methods for the preparation of tritylllithium are described and compared; yields to 100% have been realized. Tritylllithium and benzophenone react in tetrahydropyran to furnish the *para*-condensation product *p*-(diphenylmethyl)diphenylhydroxymethylbenzene (1); no normal addition is observed. Evidence for the instability of the pentaphenylethoxide ion is presented, based on the reactions of phenyllithium with benzopinacolone and methyl triphenylacetate; in both cases cleavage involving elimination of the trityl group is observed and triphenylmethane and triphenylcarbinol are usually obtained.

This study of the preparation and reactions of tritylllithium is an extension of earlier investigations with the reagent.[2] Tritylllithium has been employed as a proton-abstracting reagent, as in the preparation of enolates.[3] Its utility for this purpose is due to the difficulty with which the reagent participates in addition reactions.

In our earlier work, preparation of tritylllithium by direct reaction of trityl chloride with lithium afforded yields of the reagent up to 70% in 1,2-dimethoxyethane (DME) as solvent. Yields were determined by measuring triphenylacetic acid formed following carbonation. The chief disadvantage of this preparative method is the competitive self-condensation of the reagent producing the *p*-(diphenylmethyl)triphenylmethylbenzene anion. We have refined the original technique of metalation of triphenylmethane with butyllithium,[4] making the reaction quantitative using tetrahydrofuran or tetrahydro-2-methylfuran as solvent.

A variety of organolithium reagents can be used to effect the metalation and their rates of reaction with triphenylmethane have been measured.[5] In addition, other methods for the preparation of tritylllithium are now known.[6,7] We recommend the butyllithium exchange procedure in preference to the other methods by virtue of the high and reproducible yields, the short reaction periods, and the absence of side products. If the exchange is carried out at room temperature, excess butyllithium is rapidly consumed by reaction with tetrahydrofuran.[5,8] If butyllithium is prepared using lithium in a solvent such as tetrahydrofuran, an excess of lithium should be avoided because of reducing nature of the mixture. We have noted that benzophenone is reduced by the action of lithium in tetrahydrofuran to form both benzohydrol and benzopinacol.[9]

We attempted to condense the bulky tritylllithium reagent with several other large molecules. The reaction with benzophenone seemed significant since this ketone has no enolizable hydrogen atoms to react with the reagent.[10] Neither tritylsodium nor the trityl Grignard reagent condenses with benzophenone; with tritylsodium a color change is observed but no products are noted,[11] while the Grignard reagent reduces the ketone to benzopinacol.[12] In the present work using tetrahydropyran as solvent, tritylllithium was found to react with benzophenone to form *p*-(diphenylmethyl)diphenylhydroxymethylbenzene (1). No evi-



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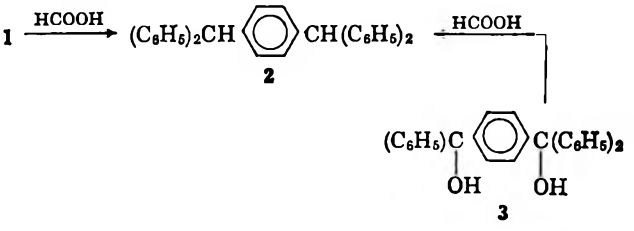
dence for any other alcohol was found following chromatographic separation of the reaction products. Condensation of the trityl reagent at the *para* position has been previously noted: self-condensation yields *p*-(diphenylmethyl)triphenylmethylbenzene,[2] and tritylsodium is reported to react with ethyl benzoate in the presence of triphenylaluminum to furnish *p*-(diphenylmethyl)benzophenone.[13] A careful examination of the carbonation product of the tritylllithium reagent showed no evidence for the *para*-condensation product, *p*-(diphenylmethyl)benzoic acid, which should be easily detectable by infrared analysis in the presence of triphenylacetic acid. Chemical structure proof for alcohol 1 was obtained by formic acid reduction to the known *p*-bis(diphenylmethyl)benzene, which was also prepared from *p*-bis(diphenylhydroxymethyl)benzene by reduction. Supporting spectral evidence for the



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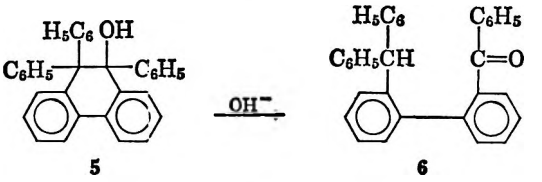
proposed structure for alcohol 1 included infrared absorption bands similar to those of triphenylcarbinol and mass spectral data which established the molecular weight and included peaks due to fragmentation on either side of the *para*-substituted ring. This chemical reactivity of a *para* position in tritylllithium is consistent with the evidence for high charge on the *para* position of tritylllithium. Sandel and Freedman[14] concluded from pmr studies that interelectron repulsion

(1) National Science Foundation Undergraduate Research Participant.
(2) P. Tomboulian, *J. Org. Chem.*, **24**, 229 (1959).
(3) H. O. House and B. M. Trost, *ibid.*, **30**, 1341 (1965).
(4) H. Gilman and R. V. Young, *ibid.*, **1**, 315 (1936).
(5) R. Waack and P. West, *J. Amer. Chem. Soc.*, **86**, 4494 (1964).
(6) P. T. Lansbury and R. Thedford, *J. Org. Chem.*, **27**, 2383 (1962); H. Gilman and B. J. Gaj, *ibid.*, **28**, 1725 (1963).
(7) J. J. Eisch and W. C. Kaska, *ibid.*, **27**, 3745 (1962).
(8) After 1 hr at room temperature, 71% of butyllithium initially present has disappeared: H. Gilman and B. J. Gaj, *ibid.*, **22**, 1165 (1957). Tritylllithium is remarkably stable in diethyl ether [H. Gilman, A. H. Haubein, and H. Hartzfeld, *ibid.*, **19**, 1034 (1954)], although it is much less stable in tetrahydrofuran.[7]
(9) The anomalous reaction of benzaldehyde with tritylllithium in this mixture is probably due to the same property.[2]
(10) *Cf.* reaction with cyclohexanone[2] and with other ketones.[3]
(11) W. Schlenk and E. Bergmann, *Ann.*, **464**, 1 (1928).
(12) W. E. Bachmann, *J. Amer. Chem. Soc.*, **53**, 2758 (1931).
(13) G. Wittig and O. Bub, *Ann.*, **566**, 113 (1950).
(14) V. R. Sandel and H. H. Freeman, *J. Amer. Chem. Soc.*, **85**, 2328 (1963).

causes dispersion of charge to the extremities of the ion resulting in high charges on the *meta* (0.08 unit of charge) and *para* (0.13 unit) positions.

Reaction of trityllithium with benzophenone at a *para* position on one ring is thus strongly favored over reaction at the benzyl position. The latter would result in the sterically crowded pentaphenylethoxide ion; no evidence for an hydrolysis product of this ion was detected. To obtain further evidence for the stability of such an ion, the reaction between phenyllithium and benzopinacolone was examined carefully. Mosher and Huber[15] investigated this system and noted that the main products were triphenylmethane and triphenylcarbinol, with traces of benzophenone. In a number of trials with this reaction, our observations agree with those above. With an excess of phenyllithium, the only products are triphenylmethane and triphenylcarbinol. In the case of inverse addition at −65° with an excess of benzopinacolone, small amounts of triphenylmethane and triphenylcarbinol are obtained, along with the starting materials. No other crystalline products were isolated; no evidence was found for benzophenone or alcohol **1**. Thus, if formed initially, the pentaphenylethoxide ion (**4**) undergoes rapid elimination of the trityl anion. (Elimination possibly occurs by direct displacement without the formation of alkoxide **4**.) Addition of 1 mol more of phenyllithium occurs preferentially with the more reactive ketone, benzophenone, so that no appreciable quantities of benzophenone accumulate in the mixture.

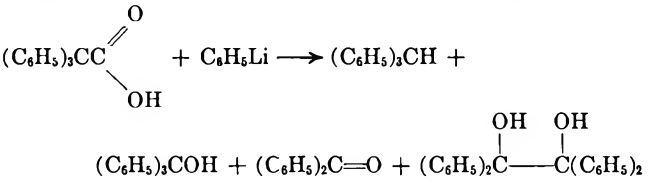
In several similar systems, cleavage reactions have been noted. Instability due to steric crowding has been established in the polyphenylethane series. Pentaphenylethane, although not so reactive as hexaphenylethane, is split by the action of heat, hydrogen iodide, sodium–potassium alloy, and bromine.[16] We verified these observations by examining the action of bromine, N-bromosuccinimide, and chlorine on pentaphenylethane; only cleavage products were obtained. Polyphenylethoxide ions are similarly unstable, especially under basic conditions when steric strain may be relieved by elimination of a stabilized leaving group. Sodium 1,1,2,2-tetraphenylethoxide decomposes to furnish benzophenone and diphenylmethane.[17] The methyl Grignard reagent reacts with benzopinacolone to yield the addition compound acetophenone and the cleavage product triphenylmethane.[18] Similarly, lithium aluminum hydride treatment of benzopinacolone in pyridine results in extensive decomposition, forming triphenylmethane and benzyl alcohol, presumably *via* a 1,2,2,2-tetraphenylethoxide ion intermediate.[19] If the leaving group in such crowded systems is bonded at another site, the tendency for cleavage is decreased and bridged pentaphenylethoxide ions are much more stable. For instance, 9,10,10-triphenyl-9,10-dihydro-9-phenanthrol (**5**) is formed in high yield using phenyllithium.[20] Although inert to phenyllithium, this pentaphenylethanol analog may be decomposed by treatment with potassium hydroxide in ethanol to yield the ketone **6**.[21] Evidence that this is a



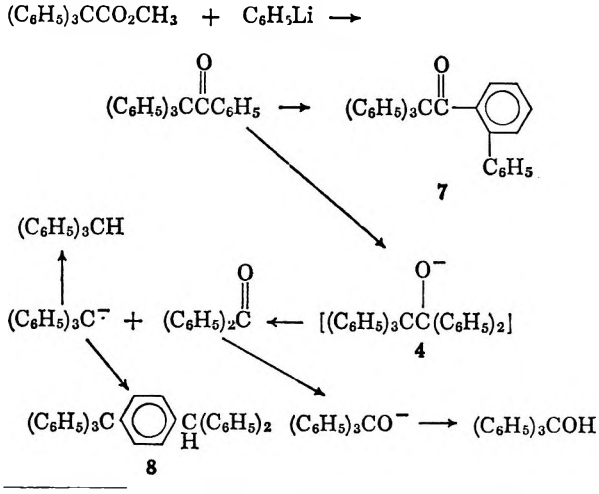
5 **6**

base-catalyzed reaction was obtained by measuring decomposition rates in Pyrex and quartz tubes. The half-life of alcohol **5** at 275° is 7.5 min in a Pyrex tube and 60 min in a quartz tube.

The recent report[22] of the condensation of phenyllithium with triphenylacetic acid or methyl triphenylacetate to form pentaphenylethanol prompted us to investigate this system under a variety of conditions. It is now clear[23] that the compound originally reported as pentaphenylethanol (mp 143–144°) is actually alcohol **1** (mp 141–142°), although we were unable to isolate any alcohol **1** from the reaction. A combination of chromatographic techniques and quantitative infrared methods was employed to analyze the reaction products. The reaction of triphenylacetic acid with excess phenyllithium yields mainly triphenylcarbinol



and triphenylmethane, with some benzophenone and benzopinacol. Because of variations in the yields of the products obtained, the reaction of methyl triphenylacetate with phenyllithium was also investigated. Once again the results were in accord with predictions based on the reaction of phenyllithium with benzopinacolone, except that some conjugate addition and self-condensation were observed. With excess phenyl-



(15) W. L. Huber, Ph.D. Thesis, University of Delaware, 1950.

(16) W. E. Bachmann, *J. Amer. Chem. Soc.*, **55**, 3005 (1933).

(17) P. J. Hamrick, Jr., and C. R. Hauser, *ibid.*, **81**, 2096, 3144 (1959). The condensation of sodium diphenylmethide with benzophenone was found to involve a rapid reversible condensation; instantaneous acidification of the mixture furnished 1,1,2,2-tetraphenylethanol, but gradual acidification resulted in the recovery of starting materials. See also W. G. Kofron, W. R. Dunnavant, and C. R. Hauser, *J. Org. Chem.*, **27**, 2737 (1962).

(18) W. A. Mosher, T. H. Fairbanks, Jr., and L. J. Prucino, Abstracts, 126th National Meeting of the American Chemical Society, New York, N. Y., Sept 1954, p 91-O.

(19) P. T. Lansbury, *J. Amer. Chem. Soc.*, **83**, 429 (1961). Elimination of the trityl anion was established by trapping with benzyl chloride to form 1,1,1,2-tetraphenylethane; see ref 6.

(20) R. C. Fuson and P. Tomboulian, *ibid.*, **79**, 956 (1957).

(21) W. A. Mosher and M. L. Huber, *ibid.*, **73**, 795 (1951).

(22) G. A. Olah, C. U. Pittman, Jr., E. Namanworth, and M. B. Comisarow, *ibid.*, **88**, 5571 (1966).

(23) G. A. Olah, private communication.

lithium, no benzopinacolone or benzophenone was found and the only products isolated were ketone **7** (16%), triphenylmethane (39%), hydrocarbon **8** (6%), and triphenylcarbinol (69%). When the phenyllithium reagent was not in excess, some starting material was recovered (25%) along with the reaction intermediates benzophenone (3.3%) and benzopinacolone (31%); triphenylmethane (24%), ketone **7** (4.8%), and triphenylcarbinol (31%) were also found. Some yellow polar carbonyl compounds were present, probably intermediates in the formation of ketone **7**.[21] The material balance indicates that no significant reaction product has been undetected in the analysis. These findings are completely consistent with the reaction pathway described above and lend further support to the hypothesis concerning the instability of the pentaphenylethoxide ion.

Experimental Section

Melting points are corrected. Microanalyses were performed by Clark Microanalytical Laboratory, Urbana, Ill., and Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were measured in carbon disulfide solution (unless otherwise indicated) with Beckman IR-5 and IR-12 spectrophotometers.

Ethereal solvents were distilled from lithium aluminum hydride into the reaction flask. An argon atmosphere was employed in all tritylllithium reactions. Purification of the argon was accomplished best by passing it through a benzophenone–lithium ketyl mixture in the ether used for the reaction.

Preparation of Tritylllithium.—A summary of the methods and conditions is presented in Table I. Results with commercial butyllithium seemed to be slightly less reproducible than those in which the butyllithium was prepared by direct reaction of lithium with butyl chloride in the reaction solvent.

TABLE I

YIELDS OF TRITYLLITHIUM

Excess of BuLi, %	Solvent[a]	Reaction time, hr	Temp, °C	Yield, %
150	THF	2	−25 to 25	100
50	TH2MF	24	25	100
25	THP	20	25	90
300	DME	1.5	25	50
50	TH2,5DMF	8	15	11
30	Dioxane	3	15	14

[a] THF is tetrahydrofuran, TH2MF is tetrahydro-2-methylfuran, THP is tetrahydropyran, DME is 1,2-dimethoxyethane, TH2,5DMF is tetrahydro-2,5-dimethylfuran.

Yields of tritylllithium were determined by weighing the triphenylacetic acid formed following carbonation of the reagent.[2] Fractional crystallization of many samples of the carbonation product did not reveal the presence of an acid other than triphenylacetic acid, as indicated by infrared analysis.

***p*-(Diphenylmethyl)diphenylhydroxymethylbenzene (1) by Reaction of Tritylllithium with Benzophenone in Tetrahydropyran.**—In a typical experiment, tritylllithium was prepared from 6.13 g (25.1 mmol) of triphenylmethane and a 10% excess of *n*-butyllithium in 50 ml of tetrahydropyran at 15° during a 3-hr reaction period. To the reagent, 2.36 g (13.0 mmol) of solid benzophenone was added. After 9 hr at 21–25°, dilute hydrochloric acid was added to the deep red mixture. The organic layer was removed by methylene chloride extraction. Following distillation of the solvents, the yellow oily product was subjected to chromatography on Alcoa F-20 alumina. Triphenylmethane (3.88 g) and *p*-(diphenylmethyl)triphenylmethylbenzene (0.40 g) were obtained in the early fractions. Elution with ether furnished the alcohol **1** (1.85 g, 33% yield based on benzophenone), mp 130–135°. Recrystallization from hexane furnished the analytical sample, mp 141–142° with decomposition. (The crystalline alcohol has a marked tendency to trap benzene and carbon tetrachloride; removal of these solvents *in vacuo* is slow.)

Anal. Calcd for $C_{32}H_{26}O$: C, 90.10; H, 6.14. Found: C, 89.87, 90.35; H, 5.90, 6.50.

The infrared spectrum closely resembles that of triphenylcarbinol, with the addition of bands at 2880 (benzylic C–H), 1022, 840, 805, 732, 662, 607, and 510 cm^{-1}. The mass spectrum[24] exhibited a parent peak (M) at *m/e* 426; other principal peaks occurred at *m/e* 409 (M − OH), 349 (M − C_6H_5), 271 (M − $2C_6H_5$), and 259 [M − $(C_6H_5)_2CH$]. The pmr spectrum[24] had peaks for aromatic hydrogens at 7.26 and 7.19 (24 H), for a benzylic hydrogen at 5.53 (1 H), and for an hydroxyl proton at 2.77 (1 H).

Stability of Alcohol 1 to Base.—The effects of a variety of bases on the alcohol **1** were examined. Decomposition was detected by infrared analysis of the reaction products recovered from the base treatment. No decomposition was detected after (1) heating at 305° for 5 min in a soft glass tube, (2) heating to 255° for 4 min with powdered potassium hydroxide, (3) boiling for 16 hr in ethanol with sodium ethoxide, and (4) stirring with an excess of butyllithium at 25° for 2 days in hexane.

Reduction of Alcohol 1 with Formic Acid.—A 0.105-g sample of the alcohol **1** was heated under reflux with 0.5 ml of toluene and 3.0 ml of 98% formic acid for 4 hr. Removal of the solvent furnished 0.074 g of solid with mp 163–170°. Crystallization from hexane or sublimation yielded needles, mp 176–177°. Mixture melting point determinations and infrared comparisons of this hydrocarbon with authentic *p*-bis(diphenylmethyl)benzene (**2**) showed the two to be identical.

***p*-Bis(diphenylhydroxymethyl)benzene (3)** was prepared by treatment of 2.20 g (0.0113 mol) of dimethyl terephthalate with excess (0.06 mol) phenyllithium in 100 ml of ether for 20 hr at reflux temperature. The crude diol product (5.07 g) was crystallized from benzene, mp 167–170° (lit.[25,26] mp 170–171°, 175°). Infrared maxima (fluorocarbon mull) were at 2.89 (OH) and 12.1 μ (*para*-substituted benzene).

***p*-Bis(diphenylmethyl)benzene (2)** was prepared by boiling 0.92 g of the above diol with 7 ml of 98% formic acid and 3 ml of toluene for 8 hr. Removal of the solvent produced the hydrocarbon, mp 175.5–177° (lit.[27] mp 171°). The infrared spectrum resembled that of triphenylmethane with the addition of bands at 1022, 842, 793, 719, and 510 cm^{-1}.

The reaction of phenyllithium with benzopinacolone was repeated over 20 times with a variety of conditions and solvents. Product analysis employed gas–liquid partition and column chromatographic techniques, plus infrared analysis.

In a typical reaction at 30°, 1.20 g (2.9 mmol) of benzopinacolone dissolved in 20 ml of benzene was added to an excess (50 mmol) of phenyllithium in 30 ml of ether. The mixture turned first yellow, then dark red-brown. After 1.5 hr, hydrolysis was effected by addition to an ice–ammonium chloride mixture. Chromatographic separation of the products furnished triphenylmethane, triphenylcarbinol, and a trace amount of benzopinacolone. No other crystalline compounds were obtained; infrared analysis of the crude reaction product as well as chromatographic fractions did not indicate the presence of other materials. In similar reactions, gas–liquid partition chromatographic analysis did not disclose any additional compounds.

In an experiment involving inverse addition, 13 mmol of phenyllithium in 10 ml of ether and 20 ml of toluene was slowly added to 3.70 g (10.5 mmol) of benzopinacolone in 60 ml of toluene while the mixture was held in a Dry Ice bath at −65°. After 15 min, the mixture was added to dilute acetic acid. The crude reaction product was treated with a benzene–ligroin mixture and filtered. The insoluble fraction was unchanged benzopinacolone. The filtrate was concentrated and subjected to chromatography on alumina. (Infrared analysis of this fraction indicated an alcoholic component in addition to the ketone.) Triphenylmethane, benzopinacolone, and triphenylcarbinol were isolated in small quantities as crystalline compounds; no other crystalline components were obtained and no evidence for benzo-

(24) The mass spectra were measured on an Hitachi RMU-6A instrument with a source temperature of 200°. We are indebted to Mr. Ronald Hites of the Massachusetts Institute of Technology for these spectral determinations. The pmr spectrum was determined in deuteriochloroform solution on a Varian Associates A56-60 spectrometer. Chemical shifts are reported in parts per million downfield from TMS. We are indebted to Mr. Steven Beare of the University of Illinois for this determination.

(25) G. J. Sloan and W. R. Vaughan, *J. Org. Chem.*, **22**, 750 (1957).

(26) R. A. Benkeser and W. Schroeder, *J. Amer. Chem. Soc.*, **80**, 3314 (1958).

(27) E. D. Bergmann, *ibid.*, **75**, 2761 (1953).

phenone was found. Trace amounts of phenolic oils and a carbonyl compound (absorption at 1735 cm^{-1}) were found in milligram quantities in the last (polar) fractions.

Attempted Halogenation of Pentaphenylethane.—The procedure of Bachmann[18] was followed, using bromine in carbon tetrachloride solution, and the products were examined by infrared analysis. No materials other than trityl bromide and dibromodiphenylmethane were indicated. The action of N-bromosuccinimide in carbon tetrachloride solution furnished no crystalline products. Only cleavage products were identified following photochlorination[28] with chlorine in carbon tetrachloride solution.

Decomposition of 9,10,10-Triphenyl-9,10-dihydro-9-phenanthrol (5).[20]—Small amounts of alcohol **5** were heated in both Pyrex and quartz tubes under a nitrogen atmosphere in an oil bath at 275°. Progress of the decomposition was followed by quantitative infrared spectroscopy, measuring the carbonyl band in the product (**6**). Observed half-lives were 7.5 and 60 min, respectively, in the Pyrex and quartz tubes. Essentially complete conversion to *o*-(α,α-diphenyl-*o*-tolyl)benzophenone (**6**) was observed in a Pyrex tube held at 300° for 30 min. The ketone **6** was isolated and identified by its melting point, 173–175° (lit.[21] mp 178–179°), and the infrared spectrum which exhibited typical benzophenone-type absorption bands at 1669, 1314, 1283, 1263, and 928 cm^{-1}, aliphatic CH absorption at 2900 cm^{-1}, and aromatic CH bands at 760, 753, 729, and 698 cm^{-1}.

Reaction of Triphenylacetic Acid with Phenyllithium.—In a typical reaction (one of three), 1.508 g (5.24 mmol) of triphenylacetic acid (three times crystallized from toluene) dissolved in 180 ml of ether was added to phenyllithium prepared from 7.4 ml (70 mmol) of bromobenzene. After stirring at 25° for 3 hr, the red-brown mixture was added to ice and water. Triphenylacetic acid (0.305 g) was recovered from the water layer. Removal of the organic solvent left 1.62 g of a yellow semisolid which furnished 0.42 g of crystals, mp 140–161°, upon treatment with ligroin (bp 30–60°). Infrared analysis indicated this to be mainly triphenylcarbinol, which was isolated from some of the runs (mp 160–166°). Crystallization of this impure material from benzene furnished a small amount of benzopinacol, mp 183–185°. Benzophenone and triphenylmethane were readily identified in the crystallization residues, but no other reaction products were indicated.

In the other runs, the same products were identified, although the yields were not consistently reproducible, but in no case was any evidence for alcohol **1** found.

Methyl triphenylacetate was prepared conveniently from triphenylacetyl chloride and methanol. Triphenylacetic acid, thionyl chloride, and hexane were boiled for 3 hr and the solvent was distilled below 80°. Methanol was added and the mixture was heated under reflux for 18 hr. Removal of the solvent followed by crystallization furnished 3.69 g (79% yield) of methyl triphenylacetate, mp 185–187°. An additional crystallization gave a sample with mp 187.5–189° (lit.[29] mp 185–187°). The infrared spectrum exhibits ester absorption at 1743 and 1222 cm^{-1}.

Reaction of Methyl Triphenylacetate with Phenyllithium. A.—To a solution of phenyllithium prepared from 0.100 mol of bromobenzene and 0.190 g-atom of lithium in 75 ml of ether was added 1.33 g (4.43 mmol) of the ester (mp 187.5–189°) as a slurry in 75 ml of ether. The resulting deep red mixture was stirred at 23° for 2 hr before hydrolysis was effected by addition to ice. Methylene chloride extraction furnished the crude product which was subjected to chromatographic analysis on activated Alcoa F-20 alumina. Analysis of the fractions employed gas–liquid partition chromatography (SE-30 on glass beads) and quantitative infrared spectroscopic techniques. In addition to biphenyl, the following reaction products were obtained (yields are based on the ester): triphenylmethane, 0.426 g (39%); *p*-(diphenylmethyl)triphenylmethylbenzene (**8**), 0.062 g (6%); *o*-biphenylyl triphenylmethyl ketone (**7**), 0.308 g (16%); triphenylcarbinol, 0.721 g (69%). No evidence for the presence of benzopinacolone, benzophenone, benzopinacol, or alcohol **1** was found. Products were identified by comparison with known samples.

When the reaction was repeated using four times as much ester (67 mmol of phenyllithium and 10.3 mmol of ester), essentially the same results were obtained.

B.—A freshly prepared solution of phenyllithium (17 mmol) was cooled to −70°. A slurry of 1.79 g (5.97 mmol) of methyl triphenylacetate was added in 100 ml of ether; no color change was observed. The stirred mixture was allowed to warm up to 20° during 1.5 hr and after 1 hr at 23° hydrolysis was effected with a mixture of ice and hydrochloric acid. Product analysis was by the same techniques as above: recovered ester, 0.456 g (25%); triphenylmethane, 0.344 g (24%); benzophenone, 0.036 g (3.3%); benzopinacolone, 0.646 g (31%); *o*-biphenylyl triphenylmethyl ketone (**7**), 0.125 g (4.8%); triphenylcarbinol, 0.498 g (31%). Infrared analysis did not indicate the presence of any other alcoholic compounds, except for trace amounts in the last polar fractions which were yellow oils with phenolic odors; carbonyl absorption bands (1701 and 1672 cm^{-1}) were also present.

Registry No.—Benzophenone, 119-61-9; tetrahydropyran, 142-68-7; **1**, 15591-47-6; trityllithium, 733-90-4; phenyllithium, 591-51-5; benzopinacolone, 466-37-5; triphenylacetic acid, 595-91-5; methyl triphenylacetate, 5467-21-0.

Acknowledgment.—The early phases of this research were supported by a Frederick Gardner Cottrell Grant from the Research Corporation.

(28) R. E. Lovins and L. J. Andrews, *J. Org. Chem.*, **29**, 487 (1964).

(29) A. G. Brook and H. Gilman, *J. Amer. Chem. Soc.*, **76**, 77 (1954).

The Isomerization of the Diethylbenzenes Using Zeolite Catalysts[1]

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Partially multivalent metal cation exchanged, partially decationized Type Y zeolites catalyze the isomerization of diethylbenzenes. The absence of stable zeolite catalyst–reactant complexes permits the ready formation of 1,2,4-triethylbenzene through the transalkylation of the diethylbenzenes. This isomer, which has not been reported in previous studies with Lewis acid catalysts, dealkylates to the equilibrium distributions of the diethylbenzene isomers. The formation of complexes between Lewis acid catalysts and alkyl aromatics depends upon the ring position of the alkyl groups and has likely influenced previously reported reaction mechanisms. No isomerization occurs with zeolite catalysts in the absence of transalkylation. The equilibrium product distribution at 170° consists of approximately 50 mol % transalkylate: the diethylbenzene fraction contains about 5% *ortho*, 62% *meta*, and 33% *para* isomers and the triethylbenzene fraction consists of 31% 1,2,4 and 69% 1,3,5 isomers.

Despite the large volume of work published on the isomerization of the diethylbenzenes, it is still not clear what part transalkylation plays in the final isomer distribution. Allen and Yats have demonstrated that the isomerization of alkylaromatics involves both intramolecular and intermolecular rearrangements, the relative contributions of which depend upon the structure of the alkylaromatic.[2,3] Olah, *et al.*, attribute the isomerization of diethylbenzenes solely to a sequence of intramolecular 1,2 shifts even though transalkylation accounts for as much as 40 mol % of the products.[4] On the other hand, Unseren and Wolf have shown that 1,2 shifts can only compete with transalkylation and that ethylbenzene transalkylates more rapidly than it isomerizes.[5] It is important to note that all previous investigations failed to isolate and appreciate the importance of the 1,2,4-trisubstituted isomer in the transalkylation products.

It is generally agreed that the alkylation of aromatic hydrocarbons and the related isomerization and transalkylation of the alkyl-substituted aromatics with acidic catalysts involve electron-deficient intermediates, *i.e.*, carbonium ions. This study was undertaken with the objective of closely following the composition of the transalkylated products during the isomerization of diethylbenzenes with a crystalline catalyst derived from Type Y zeolite. It was hoped that the data would reveal the reaction path of the isomerization and subsequently shed light on the reaction mechanism and the nature of the intermediate species.

Results

Previous work has shown that the catalyst used in this study, partially multivalent cation exchanged, partially decationized Type Y zeolite possesses unusually strong catalytic activity for the alkylation of aromatic hydrocarbons with low molecular weight olefins.[6] Mineral acid promoted and nonpromoted amorphous silica–alumina catalysts require higher temperature for the transalkylation of alkyl-substituted aromatics than for alkylation. On the other hand, the zeolite catalyst is sufficiently active to catalyze isomerization and transalkylation reactions under alkylation conditions. Products rich in the *meta*-substituted isomers are frequently obtained, much the same as with promoted Lewis acid catalysts.

Initial experiments with diethylbenzenes were carried out to determine at what temperature isomerization occurs in the absence of transalkylation. Neither isomerization nor transalkylation of *p*-diethylbenzene occurred at 50°. At 100°, 2 mol % of the diethylbenzene was transalkylated to ethylbenzene and triethylbenzene, but no isomerization occurred even after a reaction time of 24 hr. The triethylbenzene fraction contained only one isomer, the 1,2,4-triethylbenzene. When the temperature was raised to 150° for 16 hr, 30 mol % of the diethylbenzene was transalkylated, accompanied by 10% isomerization of the diethylbenzene fraction. Close examination of the transalkylated products revealed the existence of two trisubstituted isomers, the 1,2,4- and the 1,3,5-triethylbenzenes, and that their relative concentrations varied through the course of the reaction. These initial results showed that isomerization does not take place in the absence of transalkylation and indicated that 1,2,4-triethylbenzene was the principal reaction intermediate. It is significant that this isomer has not been reported in previous investigations of the isomerization and transalkylation of diethylbenzenes.

Product distributions obtained in the isomerization of *o*-diethylbenzene at 170°, over a period of 100 hr, are summarized in Table I. The initial products were ethylbenzene and 1,2,4-triethylbenzene. No increase in the amounts of *para* and *meta* isomers occurred, beyond those in the starting material, until the concentration of the 1,2,4 isomer reached about 3–4 mol % of the reaction mixture after a reaction period of about 1–2 hr. During the course of the reaction, the concentration of 1,2,4 isomer in the trisubstituted fraction decreased from 100 to 34%, the balance being the 1,3,5 isomer. The over-all concentration of the former isomer passed through a maximum of 13 mol % of the reaction mixture to its equilibrium value of 9 mol %. The extent of transalkylation at equilibrium was about 50 mol % and was obtained in approximately 24 hr.

The pure *para* isomer transalkylated to about equilibrium distribution (Table II) in about the same time as the pure *ortho* isomer. The initial products were ethylbenzene and, again, the 1,2,4-trisubstituted iso-

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

(2) R. H. Allen, L. D. Yats, and D. S. Erley, *J. Amer. Chem. Soc.*, **82**, 4853 (1960).

(3) R. H. Allen, *ibid.*, **82**, 4856 (1960).

(4) G. A. Olah, M. W. Meyer, and N. A. Overchuk, *J. Org. Chem.*, **29**, 2313 (1964).

(5) E. Unseren and A. P. Wolf, *ibid.*, **27**, 1509 (1962).

(6) To be published. Paper presented by P. E. Pickert at the Meeting of the American Institute of Chemical Engineers, Columbus, Ohio, May 16, 1966.

TABLE I

THE ISOMERIZATION OF *o*-DIETHYLBENZENE AT 170°

	Product distribution, mol %						Isomer distribution (normalized)				
		Diethylbenzene			Triethylbenzene		Diethylbenzene			Triethylbenzene	
Time	Ethylbenzene	*o*	*m*	*p*	1,2,4	1,3,5	*o*	*m*	*p*	1,2,4	1,3,5
0	0	93.2	5.9	0.9	0	0	93.2	5.9	0.9		
1.5 min	0.6	92.6	5.1	1.1	0.6	0	93.7	5.2	1.1	100	0
5 min	0.8	91.9	5.6	0.8	0.9	0	93.5	5.7	0.8	100	0
20 min	1.4	90.6	5.7	0.4	1.9	0	93.7	5.9	0.4	100	0
40 min	1.6	90.1	5.7	0.7	1.9	0	93.4	5.9	0.7	100	0
60 min	2.5	86.8	6.0	1.8	2.7	0.2	91.8	6.3	1.9	94.3	5.7
2 hr	4.2	81.0	8.5	1.4	4.6	0.4	89.2	9.3	1.5	92.1	7.9
4 hr	8.6	70.8	11.4	1.6	6.7	0.9	84.5	13.6	1.9	88.0	12.0
7 hr	11.8	59.7	14.2	2.2	9.6	2.5	78.4	18.7	2.9	79.5	20.5
23 hr	24.6	12.9	27.8	9.7	13.1	12.0	25.6	55.1	19.3	52.1	47.9
32 hr	23.3	6.5	31.9	12.6	10.9	14.8	12.7	62.5	24.7	42.4	57.6
47 hr	24.5	3.9	31.1	14.8	8.9	16.8	7.8	62.5	29.7	34.6	65.4
71 hr	20.5	3.1	32.8	15.7	9.4	18.4	6.0	63.5	30.4	33.8	66.2
100 hr	20.4	3.1	33.1	15.9	9.2	18.2	6.0	63.4	30.5	33.6	66.4

TABLE II

THE ISOMERIZATION OF *p*-DIETHYLBENZENE AT 170°

	Product distribution, mol %						Isomer distribution (normalized)				
		Diethylbenzene			Triethylbenzene		Diethylbenzene			Triethylbenzene	
Time	Ethylbenzene	*o*	*m*	*p*	1,2,4	1,3,5	*o*	*m*	*p*	1,2,4	1,3,5
0	0	0	0	100	0	0					
0.5 min	0.4	0	0	99.5	0.2	0	0	0	100	100	0
2 min	0.3	0	0	99.5	0.3	0	0	0	100	100	0
5 min	0.6	0	0	99.0	0.4	0	0	0	100	100	0
10 min	0.9	0	0	98.4	0.7	0	0	0	100	100	0
20 min	1.3	0	0.1	97.7	1.0	0	0	0.1	99.9	100	0
30 min	2.3	0	0.4	95.6	1.7	0	0	0.4	99.6	100	0
60 min	3.0	0	0.6	93.8	2.6	0	0	0.6	99.4	100	0
2.5 hr	5.7	0.3	1.7	86.3	5.2	0.8	0.3	1.9	97.7	87.5	12.5
4 hr	10.4	0.3	2.7	78.4	7.0	1.2	0.4	3.3	96.3	85.9	14.1
6 hr	11.9	0.7	3.9	73.0	8.4	2.1	0.9	5.0	94.1	79.7	20.3
22 hr	22.7	1.6	15.3	39.0	11.4	10.1	2.9	27.3	69.8	53.1	46.9
46 hr	21.7	3.4	24.8	24.1	10.5	15.4	6.5	47.5	46.0	40.6	59.4
54 hr	22.0	4.1	27.0	21.5	9.7	15.6	7.8	51.2	40.9	38.2	61.8
70 hr	20.9	3.8	30.5	18.1	9.6	17.1	7.2	58.2	34.6	36.1	63.9
100 hr	20.0	2.8	32.9	18.0	8.3	18.1	5.2	61.4	33.5	31.4	68.6

mer; the 1,3,5 isomer appeared only when a substantial amount of the 1,2,4 isomer had been formed. As before, the concentration of the 1,2,4 isomer in the trisubstituted fraction decreased from 100 to 31 mol %, while the over-all concentration passed through a maximum of about 11–12 mol % before reaching its equilibrium concentration of 8 mol %. The close similarity between the transalkylation and isomerization of the *ortho* and *para* isomers suggests that the formation of the 1,2,4 isomer may be the rate-controlling step.

The isomerization of the *meta* isomer (Table III) was considerably more rapid than that of the *ortho* and *para* isomers and was essentially complete after 30 hr yielding the same isomer distributions. The shorter time required to obtain this equilibrium distribution was probably due to starting closer to the final composition, the *meta* isomer constituting over 60% of the mixture. Again transalkylation occurred to the extent of 50 mol % of the diethylbenzenes and led to the appearance of ethylbenzene and triethylbenzenes. However, with the *m*-diethylbenzene, the 1,2,4- and the 1,3,5-triethylbenzenes appeared essentially at the same time and initially closer to their equilibrium distribution. The reversibility of the transalkylation–isomerization reaction was demonstrated by using 1,3,5-triethylbenzene and ethylbenzene as starting materials (Table IV). The products were the diethylbenzene isomers in equilibrium distribution.

That the isomerization mechanism involved the formation of transalkylated products was further shown by repeating the isomerization of the *ortho* isomer in the presence of added ethylbenzene and triethylbenzene (Table V). If transalkylation contributed to isomerization, an increase in rate should result. If, however, the mechanism involved 1,2 shifts, a decrease in rate due to dilution of the reactant should occur. As expected, after 4 hr the disubstituted fraction of the reaction mixture from the pure *ortho* isomer contained 84.5% *ortho*, while that from the reaction mixture with added transalkylation products contained 76.7% *ortho*. Thus the isomerization rate was increased by the presence of the transalkylation products.

Discussion

Considerable evidence has been assembled which suggests that the mechanism of carbonium ion formation with zeolite catalysts is fundamentally different from that of conventional Lewis acid and Brønsted acid catalysts. It has been postulated that hydrocarbon molecules are polarized by the strong electrostatic fields surrounding positively and negatively charged sites

TABLE III

THE ISOMERIZATION OF *m*-DIETHYLBENZENE AT 170°

	Product distribution, mol %						Isomer distribution (normalized)				
		Diethylbenzene			Triethylbenzene		Diethylbenzene			Triethylbenzene	
Time	Ethylbenzene	*o*	*m*	*p*	1,2,4	1,3,5	*o*	*m*	*p*	1,2,4	1,3,5
0	0	0	100	0	0	0	0	100	0	0	0
2 min	0	0	100	0	0	0	0	100	0	0	0
5 min	0.1	0.1	99.3	0.3	0.2	0	0.1	99.6	0.3	100	0
20 min	0.3	0.2	98.8	0.4	0.2	0.2	0.2	99.4	0.4	50	50
40 min	0.9	0.7	96.5	1.1	0.3	0.6	0.7	98.2	1.1	30.8	69.2
2 hr	0.9	0.7	95.7	1.9	0.3	0.7	0.7	97.4	1.9	27.3	72.4
3 hr	2.7	1.4	90.1	2.4	0.9	3.5	1.5	95.9	2.6	26.8	73.2
20 hr	13.1	2.3	61.0	7.6	4.4	11.6	3.3	86.1	10.7	27.5	72.5
22 hr	15.3	1.8	58.2	8.5	4.3	11.8	2.6	84.9	12.4	26.7	73.3
31 hr	18.2	3.2	35.9	17.6	8.6	16.6	5.6	63.4	31.0	34.0	66.0
76 hr	18.9	2.9	32.9	17.3	8.5	19.5	5.4	62.0	32.6	30.4	69.6

TABLE IV

THE TRANSALKYLATION OF ETHYLBENZENE AND 1,3,5-TRIETHYLBENZENE AT 170°

		Product distribution, mol %					Diethylbenzene isomer distribution (relative)		
		Diethylbenzene			Triethylbenzene				
Time	Ethylbenzene	*o*	*m*	*p*	1,2,4	1,3,5	*o*	*m*	*p*
0 min	48.2	0	0	0	0	51.8			
1 min	48.0	0	0.1	0.2	0	51.8			
2 min	47.7	0	0.6	0.4	0	51.2			
4 min	46.8	0	0.5	0.4	0.1	52.1			
5 min	46.4	0	0.9	0.5	0.3	51.8			
10 min	45.0	0	1.5	1.0	1.5	51.9			
30 min	41.5	0.1	2.9	1.6	1.2	52.7	1	29	16
60 min	37.5	0.3	4.7	2.6	2.0	52.8	1	16	9
2 hr	33.5	0.8	10.7	5.5	3.2	46.4	1	13	7
3 hr	22.0	1.7	24.5	10.9	6.7	34.3	1	14	6
4 hr	15.5	2.4	28.6	13.2	9.1	31.2	1	12	6
5 hr	13.5	2.5	31.5	14.5	10.0	27.9	1	13	6
8 hr	14.3	2.7	32.4	14.3	10.4	25.9	1	12	5
10 hr	13.5	2.5	32.3	14.8	11.1	25.7	1	13	6

influence the reaction mechanism significantly. The preponderance of *meta*-substituted products with large, noncatalytic amounts of the halide-containing catalysts has been explained on the basis of the greater stability of the *meta* compared with similar *ortho* and *para* σ complexes.[8,9]

The experimental data obtained in this study show that starting with any one of the three diethylbenzene isomers, the same product distribution was obtained, demonstrating conclusively that equilibrium had been reached. The extent of transalkylation, at equilibrium, was the same for each isomer. The product consisted of about 20 mol % ethylbenzene, 53 mol % diethylbenzenes, and 27 mol % triethylbenzenes. The difference in concentration between the ethylbenzene and triethylbenzene fractions from the theoretical 1:1 molar ratio is explained by the transalkylation of some of the ethylbenzene to diethylbenzenes and benzene; the latter was lost from the system at reaction temperature. The diethylbenzene fraction at equilibrium consisted of about 6% *ortho*, 62% *meta*, and 32% *para* and the trisubstituted fraction of about 32% 1,2,4 and 68% 1,3,5 isomers. That the isomerization of the diethylbenzenes proceeds *via* a transalkylation mechanism is supported by the following observations. (1) Isomerization does not take place in the absence of transalkylation. (2) The rate of isomerization is increased by the addition of transalkylation products. (3) The isomer distribution in the diethylbenzene fraction formed initially

TABLE V

THE ISOMERIZATION OF *o*-DIETHYLBENZENE WITH ADDED TRANSALKYLATION PRODUCTS AT 170°

	Product distribution, mol %						Isomer distribution (normalized)				
		Diethylbenzene			Triethylbenzene		Diethylbenzene			Triethylbenzene	
Time	Ethylbenzene	*o*	*m*	*p*	1,2,4	1,3,5	*o*	*m*	*p*	1,2,4	1,3,5
0	7.9	75.9	4.0	0.7	0	11.5	94.2	4.9	0.9	0	100
1 min	9.8	74.1	4.1	0.8	0.3	10.0	93.8	5.2	1.0	2.9	97.1
5 min	10.4	72.8	4.2	0.8	0.7	11.1	93.5	5.4	1.0	5.7	94.3
10 min	10.9	72.5	4.0	0.9	0.7	11.0	93.7	5.2	1.1	6.3	93.7
60 min	10.9	68.9	6.4	1.2	2.6	10.0	90.0	8.4	1.6	20.5	79.5
2 hr	11.8	63.0	8.5	2.0	5.0	9.7	85.7	11.5	2.7	34.0	66.0
4 hr	17.0	48.5	11.9	2.7	10.0	9.7	76.7	18.9	4.3	50.8	49.2
7 hr	18.6	36.3	16.9	3.5	13.4	11.5	64.1	29.8	6.2	53.9	46.1
23 hr	20.8	13.0	27.0	10.1	13.3	15.3	25.7	53.4	19.9	46.4	53.6
30 hr	18.9	9.7	29.8	11.5	12.4	17.8	19.0	58.4	22.6	41.0	59.0
46 hr	20.4	5.7	30.0	14.3	10.4	19.1	11.4	60.0	28.6	35.3	64.7
70 hr	18.8	4.0	30.5	16.1	10.3	20.2	7.9	60.3	31.8	33.8	66.2
94 hr	18.8	2.9	32.2	17.8	9.5	18.8	5.4	60.9	33.6	33.6	66.4

associated with the crystal lattices to give quasi-carbonium ion intermediates which then react in characteristic fashion.[7] Thus the zeolite catalysts are particularly suitable for alkylbenzene isomerization since the strong complex formation between alkylaromatics and acid catalysts, such as those found with hydrogen halide-promoted Lewis acids, is not observed. These complexes play an important role in alkylation and isomerization reactions with acidic catalysts and likely

(7) P. E. Pickert, J. A. Rabo, E. Dempsey, and V. Schomaker, *Proc. Intern. Congr. Catalysis, 3rd, Amsterdam, 1964*, **1**, 714 (1965).

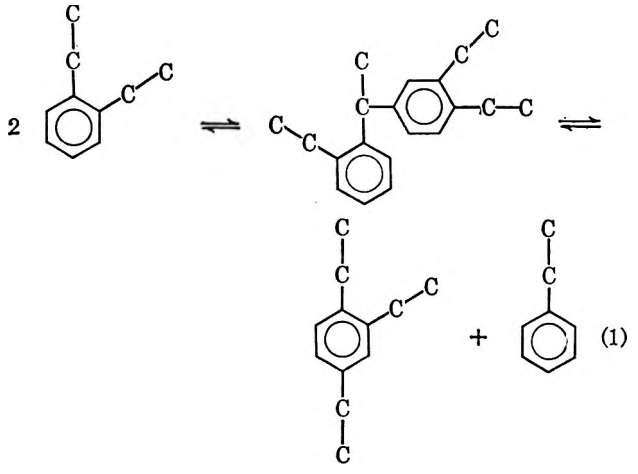
(8) S. U. Choi and H. C. Brown, *J. Amer. Chem. Soc.*, **88**, 903 (1966).

(9) H. C. Brown and J. J. Melchiore, *ibid.*, **87**, 5269 (1965).

from the reaction of 1,3,5-triethylbenzene and ethylbenzene is that found in the final isomer distribution.

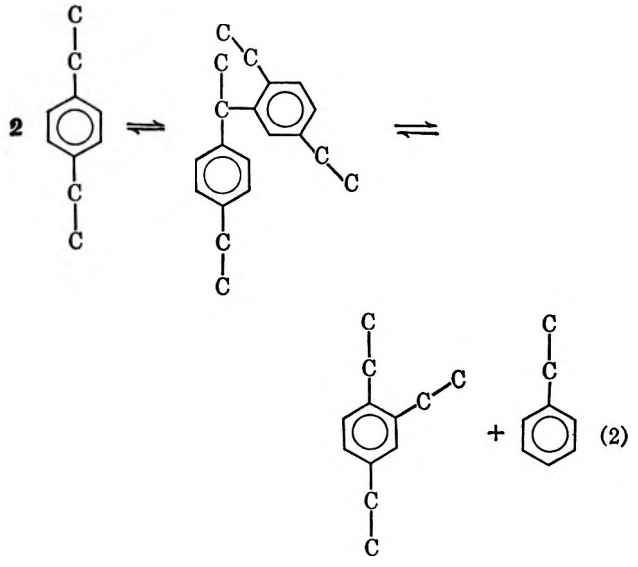
The intermolecular isomerization of the diethylbenzenes can be satisfactorily explained by a 1,1-diphenylethane-type intermediate. Such an intermediate, proposed by Streitwieser[10] and Pines,[11] would not be at variance with the data of Unseren[5] and its existence was substantiated by the recent[12] isolation of diarylalkanes from the disproportionation products of alkylbenzenes. No catalyst aging was observed in our studies which precludes the presence of ethylene as an intermediate. If ethylene were an intermediate, *sec*-butylbenzenes would have been formed with similar zeolite catalysts containing 0.5 wt % Pd as is found in the alkylation of benzene with ethylene using such catalysts. The presence of diarylalkane intermediates provides a satisfactory explanation of the experimental results obtained in our studies.

The only possible products from the transalkylation of *o*-diethylbenzene with a diarylalkane-type intermediate are 1,2,4-triethylbenzene and ethylbenzene as shown in eq 1. The absence of the 1,2,3 isomer is



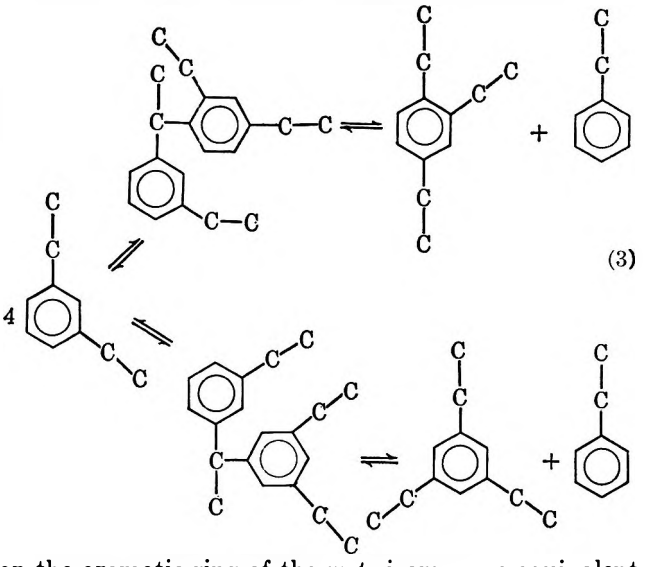
(1)

presumably due to steric considerations and the remaining positions on the aromatic ring are equivalent. From the *para* isomer (eq 2) it can be seen that the only products are again ethylbenzene and 1,2,4-



(2)

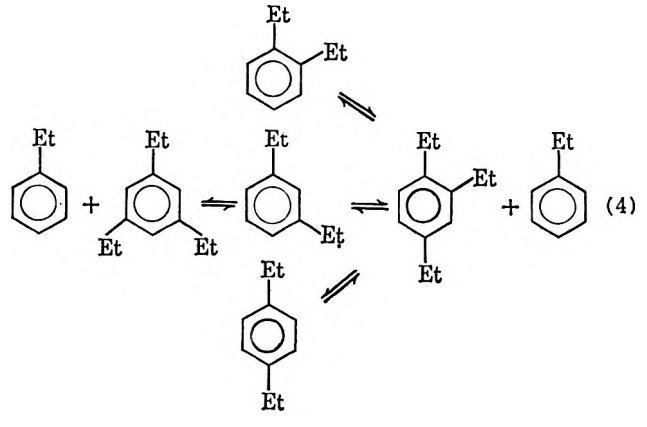
triethylbenzene, since all four unoccupied positions on the aromatic nucleus are equivalent. This is consistent with the experimental data shown in Tables I and II. Starting with the *ortho* and *para* isomers, the trisubstituted fraction initially consists exclusively of the 1,2,4-triethylbenzene. However, it is important to note that with the *meta* isomer both the 1,2,4- and the 1,3,5-triethylbenzenes can be formed as illustrated in eq 3. Two of the three available positions



(3)

on the aromatic ring of the *meta* isomer are equivalent and lead to the formation of the 1,2,4-triethylbenzene, while the third position accounts for the formation of the 1,3,5-substituted product. The data from the experiment starting with the *meta* isomer (Table III) showed both trisubstituted isomers appearing at approximately the same time. The concentration of the 1,3,5 isomer in the triethylbenzene fraction increased more rapidly starting with the *m*-diethylbenzene than with the *ortho* and *para* isomers. Starting with *o*- and *p*-diethylbenzenes, no 1,3,5 isomer appeared before a significant amount of *m*-diethylbenzene had been formed. Both these points indicate that the 1,3,5 isomer is directly derived from the *m*-diethylbenzene, although the rate of transalkylation was significantly more rapid with the *ortho* and *para* isomers. After about 2 hr with this latter compound, approximately 5% of the reaction mixture consisted of triethylbenzenes, whereas 1% was formed from the *m*-diethylbenzene.

It is now possible to describe an isomerization reaction scheme, based on a transalkylation mechanism, consistent with the experimental data and which does not require a 1,2-shift step. This scheme is summarized in eq 4.



(4)

(10) A. Streitwieser and L. Rief, *J. Amer. Chem. Soc.*, **86**, 1988 (1964).
(11) H. Pines and J. T. Arrigo, *ibid.*, **80**, 4369 (1958).
(12) R. M. Roberts, E. K. Baylis, and G. J. Fonken, *ibid.*, **85**, 3454 (1963).

The data in Table V show that, in the reaction (transalkylation) of the 1,3,5-triethylbenzene and ethylbenzene, the amount of the *m*-diethylbenzene was greater than that of the 1,2,4-triethylbenzene. This indicates that *m*-diethylbenzene was the precursor of this latter compound in this reaction. The diethylbenzene fraction was initially richer in the *meta* isomer than the final equilibrium distributions of 1:12:6, *ortho–meta–para*, since it is the only product of the dealkylation of the 1,3,5 compound as indicated in eq 4. The products obtained from the transfer of an ethyl group to the ethylbenzene reactant should be in equilibrium distribution, which is again richer in the *meta* isomer. The experimental results support these conclusions within the accuracy of the analytical measurements.

That the 1,2,4-triethylbenzene has not previously been reported[4,13] as one of the products of transalkylation using metallic halide catalysts is simply explained by the greater stability of catalyst complexes of *meta* derivatives. For example, the equilibrium leading to the formation of the 1,3,5-triethylbenzene as shown in eq 5 is shifted far to the right,[13] particularly when large, noncatalytic amounts of Lewis acid catalysts are employed.

$$(1,2,4\text{-}Et_3C_6H_3\cdot H)^+\cdot BF_4^- \rightleftharpoons 1,2,4\text{-}Et_3C_6H_3 \rightleftharpoons$$
$$1,3,5\text{-}Et_3C_6H_3 \rightleftharpoons (1,3,5\text{-}Et_3C_6H_3\cdot H)^+BF_4^- \quad (5)$$

The product distributions of both the isomerization and transalkylation reactions always agree with calculated thermodynamic equilibria with the molecular sieve zeolite catalyst. This indicates the absence of the stable catalyst–reactant intermediate complex frequently observed with conventional acid catalysts.

(13) A. P. Lien and D. A. McCauley, *J. Amer. Chem. Soc.*, **75**, 2407 (1953).

Experimental Section

The di- and triethylbenzenes were obtained from the Aldrich Chemical Co., Milwaukee, Wis., and were used without further purification. The *o*-diethylbenzene contained 93% *ortho*, 6% *meta*, and 1% *para*; the *m*- and *p*-diethylbenzenes and the 1,3,5-triethylbenzene were all 99% pure.

The reactions were carried out in a 100-ml flask, fitted with a water-cooled condenser and a magnetic stirrer. The crystalline catalyst was synthesized from Type Y zeolite with a SiO_2/Al_2O_3 molar ratio of 5.0 by partial multivalent cation exchange (40% Ce^{3+}) and partial decationization (50%). The balance of the cations was sodium. The preparation and pertinent properties of this material have been previously reported.[6] Five grams of catalyst were used/0.5 mol of reactant and the reaction temperatures were maintained using a constant-temperature oil bath. Samples were removed periodically and analyzed on a Perkin-Elmer 154 D vapor fractometer. The fractometer was equipped with a 150-ft *m*-bis(*m*-phenoxyphenoxy)benzene-coated (modified by 20% Apiezon L) capillary column and a hydrogen flame ionization detector. The 1,2,4-trialkylbenzene was characterized by both ir and uv analyses.

Retention times of ethylbenzene, diethylbenzenes, and triethylbenzenes are given in Table VI.

TABLE VI
RETENTION TIMES OF ETHYLBENZENE, DIETHYLBENZENES, AND TRIETHYLBENZENES

Compd	Retention time,[a] min
Ethylbenzene	3.7
o-Diethylbenzene	5.8
m-Diethylbenzene	5.5
p-Diethylbenzene	5.6
1,2,4-Triethylbenzene	11.2
1,3,5-Triethylbenzene	10.0

[a] At 150°; He, 30 psi.

Registry No.—Ethylbenzene, 100-41-4; *o*-diethylbenzene, 135-01-3; *m*-diethylbenzene, 141-93-5; *p*-diethylbenzene, 105-05-5; 1,2,4-triethylbenzene, 877-44-1; 1,3,5-triethylbenzene, 102-25-0.

Long-Range Effects in the Alkylation of Benzene with Dichloroalkanes[1]

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The results obtained from alkylation reactions on benzene with two series of primary chloro-containing dichloroalkanes are interpreted on the basis of a long-range effect of the reference primary chloro group on the reaction of the second chloro group. Benzene was alkylated with 1,X-dichlorooctane (*i.e.*, a mixture of the 1,1 through 1,8 isomers) using a boron trifluoride–hydrogen fluoride catalyst (a system specific for alkylation of secondary halides). The relative reaction rates for the 1,3, 1,4, 1,5, 1,6, and 1,7 isomers and the composite rate for the secondary monochlorooctanes were 1, 9.9, 23.2, 36.8, 49, and 73, respectively. The products were 7-, 6-, 5-, and 4-phenyl-1-chlorooctanes in a ratio 53:29:14:4, which was independent of the degree of dichloride conversion. The 1,1, 1,2, and 1,8 isomers did not react. The aluminum chloride catalyzed alkylation of benzene with a series of α,ω-dichloroalkanes was also examined. The rate of reaction was in the order of 1,4-dichlorobutane > 1,6-dichlorohexane > 1,5-dichloropentane > 1,3-dichloropropane and was generally slower than that of 1-chlorohexane. The higher members of this series gave the greatest amount of rearranged products from the initial reaction, but this was always less than the corresponding 1-chloroalkane. 1,4-Dichlorobutane is a special case in which anchimeric assistance by one chloro group in the ionization of the other is responsible for an increased reaction rate.

In our previously reported work on the alkylation of benzene with 1,2-dichloroalkanes using aluminum chloride, it was observed that the adjacent primary chloride had a profound effect in determining the products of reaction.[2] This report describes our work on systems in which the two chloro groups are farther apart. We have studied the effect of one chloro group on the reaction rate and products from reaction of the second chloro group. Special emphasis has been placed on the change of the effect with distance between the two chloro groups and on a comparison with the monochloroalkane reaction. Two alkylation systems have been used in this work. The alkylation of benzene with

(1) Presented at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

(2) D. L. Ransley, *J. Org. Chem.*, **31**, 3595 (1966).

1,X-dichlorooctane[3] using a hydrogen fluoride–boron trifluoride catalyst has been examined. Further, the aluminum chloride catalyzed alkylation of benzene with a series of α,ω-dichloroalkanes has been studied and compared with similar reactions of 1-chloroalkanes.

I. The Alkylation of Benzene with 1,X-Dichlorooctane.—The radical chlorination of 1-chlorooctane was taken to about 20% conversion in order to maximize the amount of dichlorooctane. The dichlorooctane fraction, when analyzed by vapor phase chromatography (vpc), showed the presence of eight compounds in the ratio 2.0:5.7:12.2:16.9:17.8:18.6:20.6:4.9.[4,5] These were presumed to be the 1,1 through 1,8 isomers, respectively.

Although it has been claimed[5] that the isomers elute from "boiling point" columns (such as the one used in this work) in order of increasing distance between the chloro groups, we wished to verify this observation.[6] The 1,1, 1,2, 1,4, 1,5, and 1,8 isomers were either synthesized or purchased. These isomers did, indeed, elute in "numerical order," and did correspond to the first, second, fourth, fifth, and eighth peaks, respectively. It therefore, seemed reasonable to assume that the third peak was the 1,3 isomer and the sixth and seventh peaks were the 1,6 and 1,7 isomers.

The alkylation of benzene was carried out by adding 2 mol of liquid hydrogen fluoride to a cold solution of 0.2 mol of 1,X-dichlorooctane in 4 mol of benzene. Boron trifluoride was bubbled through the well-stirred mixture at about 4 ml/min at 0°.

Under these conditions, the 1,1, 1,2, and 1,8 isomers did not react. This was demonstrated by the addition of external vpc standards. Hence, the 1,1, 1,2, and 1,8 isomers (together with the 1% 1-chlorooctane contaminant) could be used as internal vpc standards.

No reaction occurred for the first 30–35 min. The reaction then proceeded smoothly, although the reaction rates were different for each isomer. The rates of reaction for the various isomers were in the order 1,7 > 1,6 > 1,5 > 1,4 > 1,3.

The products of reaction were identical and showed identical distribution in each sample taken at various time intervals throughout the reaction. The products were 7-, 6-, 5-, and 4-phenyl-1-chlorooctane in the approximate ratio 53:29:14:4.

The reaction of each dichlorooctane isomer was shown to be first order in dichloride in the presence of excess benzene and hydrogen fluoride. The accuracy of the kinetic measurements for the 1,6 and 1,7 isomers was not great for these rather fast reactions. It was convenient to compare the log $([RCl_2]_0/[RCl_2]_t)$[7] values for each isomer in each sample of several runs in order to establish a relative rate scale for the reactive isomers. Taking the rate constant for the 1,3 isomers ($k_{1,3}$) as unity, we observed $k_{1,3} = 1$, $k_{1,4} = 9.9$, $k_{1,5} = 23.2$, $k_{1,6} = 36.8$, $k_{1,7} = 49$.

The same reaction was run in competition with a mixture of 1-, 2-, 3-, and 4-chlorooctanes[8] (the 1-chlorooctane not reacting). In an example the first-order rate constants (sec^{-1}) obtained by direct measurement were $k_{mono} = 5.8 \times 10^{-3}$, $k_{1,7} = 4.1 \times 10^{-3}$, $k_{1,6} = 2.92 \times 10^{-3}$, $k_{1,5} = 1.73 \times 10^{-3}$, $k_{1,4} = 7.95 \times 10^{-4}$, $k_{1,3} = 7.12 \times 10^{-5}$, the very slight (but detectable) rate differences of the isomeric monochlorooctanes being ignored, a composite value being used in this study.

Further control reactions were also run. The reaction of 1,5-dichlorooctane alone was shown to be first order in dichloride and gave the same products and distribution as did 1,X-dichlorooctane. No isomerization of the dichlorooctane occurred prior to alkylation.

A mixture of 7-, 6-, 5-, and 4-phenyl-1-chlorooctane (37.9, 36.7, 20.5, and 5.0%, respectively) was subjected to the reaction conditions, but the rate of isomerization was very slow.

The reaction of a 1-, 2-, 3-, and 4-chlorooctane mixture or of 2-chlorooctane yielded identical products for reactions of equal duration. However, gradual product isomerization from 29.6, 34.3, and 36.2% of 2-, 3-, and 4-phenyloctane initially to 39.6, 31.8, and 28.6%, respectively, after 6.5 hr was observed.

II. The Alkylation of Benzene with α,ω-Dichloroalkanes.—The aluminum chloride catalyzed alkylation reactions of benzene with 1,3-dichloropropane, 1,4-dichlorobutane, 1,5-dichloropentane, and 1,6-dichlorohexane have been studied. Product distribution and rate characteristics have been examined and compared with similar reactions of 1-chloroalkanes.

The products from the reactions of the dichloroalkanes are readily predictable from previous studies of these or similar[2,9] systems or the corresponding dibromides.[10] The reactions were carried out with 5 mol % aluminum chloride at 0–5° in excess benzene for 2 hr. The product distribution for each reaction is shown in Chart I.

The products are formed *via* an initial reaction which proceeds without rearrangement (path A, Chart I) or with rearrangement (path B). Computation of the amount of product formed *via* path A (as opposed to path B) is complicated by the subsequent reactions of the initially formed phenylchloroalkanes. Further examination of the reactions of these compounds under similar conditions was undertaken. It was assumed that the phenylchloroalkanes would behave as reactants in the same manner as when formed in the α,ω-dichloroalkane reactions. Therefore, one may proportionate the products between paths A and B.

3-Phenyl-1-chloropropane (I) gave the diphenylpropanes, III, IV, and V, in the ratio 23.5:72.2:4.3. Since I yields 23.5% III and 4.3% V while forming 72.2% IV, it is inferred that 16.0% III and 3.0% V[11] would be formed *via* path A during formation of 51.8% IV. 5-Phenyl-1-chloropentane (XII) was isolated from the reaction of 1,5-dichloropentane and its behavior under alkylation conditions examined on a small scale. Approximately the same amount of XIV as the

(3) X indicates a chloro group on each carbon, *i.e.*, a mixture of 1,1-, 1,2-, . . ., and 1,8-dichlorooctane isomers.

(4) Before distillation the ratio of products was 2.0:6.1:11.8:15.6:16.8:18.5:19.8:9.4. This is slightly, but significantly, at variance with the work of Colebourne and Stern.[5]

(5) N. Colebourne and E. S. Stern, *J. Chem. Soc.*, 3599 (1965).

(6) Colebourne and Stern[5] isolated the isomers by preparative vpc and used nmr to distinguish between the isomers. It was not clear to us how, for instance, 1,4- and 1,5-dichlorooctane could be readily distinguished by nmr.

(7) $[RCl_2]_0$ = dichloride (or monochloride) concentration at time zero; $[RCl_2]_t$ = dichloride concentration at time t.

(8) Obtained by monochlorination of *n*-octane.

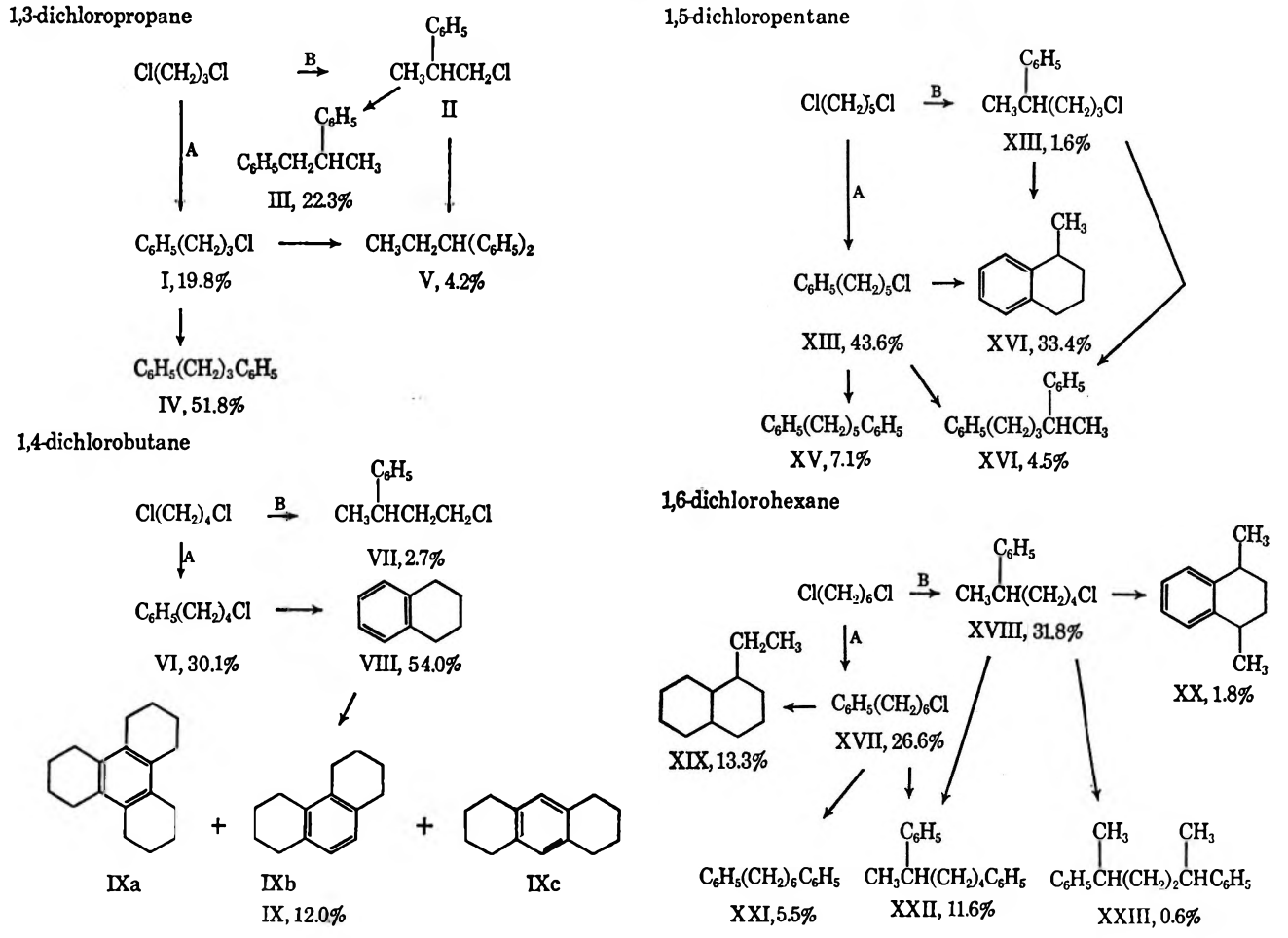
(9) K. M. Shadmanov, *Dokl. Akad. Nauk Uz. SSR*, No. 11, 37 (1957); *Chem. Abstr.*, **53**, 5214*f* (1959).

(10) H. Nozaki, M. Okazaki, N. Yamae, Y. Nishikawa, T. Hisida, and K. Sisido, *J. Org. Chem.*, **30**, 1303 (1964).

(11) 51.8/72.2 × 22.3 = 16.

CHART I

PRODUCTS FROM THE ALKYLATION OF BENZENE WITH α,ω-DICHLOROALKANES



sum of diphenylpentanes XV and XVI was formed. This would suggest that all XV and XVI were formed *via* path A. This is consistent since the closure of 4-phenyl-1-chloroalkanes is known to proceed with ease[2,12] and with little diphenylalkane formation. Compound XVII yielded 36.4% XIX, 31.4% XXI, and 25.5% XXII. The conclusion is that 2% XXII is formed *via* path A.

In Table I there is listed the proportion of products formed *via* paths A and B which is also compared with the amount of unrearranged (i.e., amount of 1-phenylalkane) and rearranged product from the identical reaction of the corresponding 1-chloroalkane.

Attempts were made to compare the rates of reactions of the dichloroalkanes with that of the monochloralkanes. However, the early experiments showed no reactions to which any kinetic order could be assigned. It appeared that there was gradual deactivation of the catalyst throughout each run. The deactivation effect was not the same for each reactant. It is possible that the catalyst is deactivated by complexing with the reaction products thereby accounting for the difference in degree of the deactivation effect.

Competition rate studies were then examined. To facilitate analysis 1-chlorohexane was used as the standard monochloroalkane, and any small differences between the C_3, C_4, C_5, and C_6 chloroalkanes were neglected. The competition reactions of 1-chlorohexane with each dichloroalkane were carried out separately and with a mixture of all four dichloroalkanes. In each reaction it was observed that the ratio of the log $[RCl_2]_0/[RCl_2]_t$[7] function remained constant throughout the run. The treatment given, therefore, was that of a reaction first order in dichloroalkane (or monochloroalkane), the deviation being ascribed to catalyst deactivation. In this manner an estimate for the relative first-order rate constants was achieved. Setting the first-order rate constant ($k_{1,3}$) for the 1,3-dichloropropane reaction as unity, the relative rates were $k_{1,3} = 1$, $k_{1,4} = 108$, $k_{1,5} = 24$, $k_{1,6} = 45$, $k_{mono} = 50$.

TABLE I

REARRANGEMENT IN THE ALKYLATION OF BENZENE WITH MONO- AND DICHLOROALKANES

	Products,[a] wt %		
Reactant	Path A unrearranged	Path B rearranged	Ambiguous
1-Chloropropane	44.4	55.6	
1,3-Dichloropropane	90.6[b] (71.6)	7.5(0.0)	1.9(28.4)
1-Chlorobutane	36.0	60.6	
1,4-Dichlorobutane	96.1[c] (96.1)	2.7(2.7)	1.2(1.2)
1-Chloropentane	40.5	59.5	
1,5-Dichloropentane	66.8[d] (50.7)	23.4(1.6)	9.8(47.7)
1-Chlorohexane	32.5	67.5	
1,6-Dichlorohexane	47.4[e] (45.4)	49.8(39.6)	2.8(15.0)

[a] Figures in parentheses show results when subsidiary phenylchloroalkane experiments are ignored. [b] I, 19.8%; IV, 51.8%; III, 16.0%; V, 3.0%: total 90.6%. [c] VI, 30.1%; VIII, 54.0%; IX, 12.0%: total 96.1%. [d] XII, 43.6%; XV, 7.1%; XIV, 11.6%; XVI, 4.5%: total 66.8%. [e] XVII, 26.6%; XIX, 13.3%; XXI, 13.3%; XXU, 5.5%; XXII, 2.0%: total 47.4%.

(12) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **31**, 89 (1966).

The value given for $k_{1,3}$ is little more than an estimate, owing to the errors introduced by competition experiments with reactants with vastly different rates.

Discussion

In this work an attempt has been made to isolate the effect of a primary chloro group on the reaction of a second chloro group in the same molecule. Particular emphasis has been placed on the effect as a function of the number of carbons separating the two chloro groups.

It may be observed that in both systems the rate of reaction of dichloroalkanes increases as the distance between the two chloro groups is increased but is slower than the corresponding monochloroalkane. The exception to these generalizations is the reaction of 1,4-dichlorobutane.

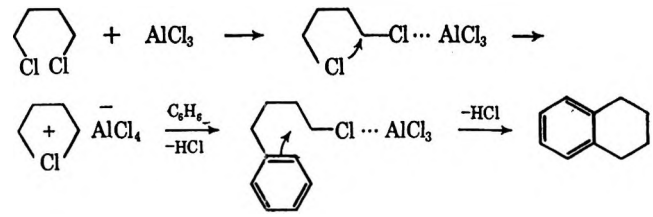
In the HF–BF_3-catalyzed reactions, the products from 1,X-dichlorooctane show a strong tendency for phenyl attachment at secondary positions most distant from the unreactive primary chloride. In contrast, the monochloroalkanes form products with random phenyl attachment to the secondary carbons.

The α,ω-dichloroalkanes undergo initial reaction with less rearrangement than the corresponding monochloroalkanes, the difference decreasing as the distance between the chloro groups is increased.

These generalized observations may be interpreted as being due to an electron-withdrawing influence of the reference primary chloro group on the reaction of the other chloro group. As the distance between the two chloro groups is increased, the influence is decreased.

The alkylation reaction involves ionization of a chloro group with generation of at least a partial positive charge. This would be a higher energy process in the presence of an electron-withdrawing influence. Rearrangement in reactions of the α,ω-dichloroalkanes would necessitate transfer of at least a partial positive charge to a carbon closer to the unreacted chloro group. This process would also be energetically less favorable when the influence of the chloro group is stronger. In contrast, rearrangement away from the primary chloro group in the reaction of 1,X-dichlorooctane is favorable. By this process the destabilizing influence of the unreactive primary chloride is decreased.

The reaction of 1,4-dichlorobutane is considered to be a special case. This reaction does not fit into the general pattern of a gradual rate change in the α,ω-dichloroalkane series. Further, the reaction rate is faster than the primary monochloroalkane and gives less rearranged product than would be anticipated on the basis of the above interpretation. It is believed that ionization of 1,4-dichlorobutane occurs with anchimeric assistance of the remaining chloro group, thereby generating a five-membered cyclic chloronium ion.[13–16] After alkylation on benzene the favored phenyl participation[2] in ionization of the remaining chloro group assists in maximizing the amount of product formed *via* the unrearranged route. This sequence may be pictured as shown.



Evidence for similar chloronium ion formation has been demonstrated by Peterson.[13–16]

It is observed that 1,6-dichlorooctane reacts more slowly than the secondary monochlorooctanes and that 1,6-dichlorohexane reacts more slowly than 1-chlorohexane and gives less rearranged products. It is therefore apparent that the influence of the reference primary chloro group is effective at least six methylene groups removed from the reaction site.

The closest analogies to this observation are the studies of Peterson and his coworkers[15] and of Stevenson and Williamson.[17] Peterson observed that there was a gradual change in reaction rate for the addition of trifluoroacetic acid to $Cl(CH_2)_nCH{=}CH_2$ as n is increased. He observed that the chloro group has an influence at distances 11 carbons removed, although he attributed the magnitude of this influence to be a facet of his particular system. Stevenson and Williamson observed a gradual change in pK for a series of cyanoamines, with the functional groups separated by as many as five methylene groups.

Both of these groups of workers interpret their results as due to a long-range inductive effect of the chloro and the cyano group, respectively. As a test of their theory they plot log (log F_u − log F_s) (where F_u = the function for the unsubstituted case and F_s for the substituted case) against the number of methylene groups separating the substituent from the critical reaction site. This treatment has been widely discussed and largely accepted.[13–26] Both research groups find linear correlations. An attenuation factor for the change in the effect per methylene may therefore be reached. Attenuation factors of 0.3 to 0.55[18–28] have been previously used or calculated. Stevenson and Williamson find 0.5 to be the attenuation factor and Peterson 0.65.

A similar treatment may be used for the rates of reaction of the 1,X-dichlorooctane series. A good linear plot was obtained using the data for the monochlorooctane and the 1,3-, 1,4-, 1,5-, 1,6-, and 1,7-dichlorooctanes.[29] The attenuation factor was found to be 0.58.

(13) P. E. Peterson and G. Allen, *J. Amer. Chem. Soc.*, **85**, 3608 (1963).
(14) P. E. Peterson and E. V. P. Tao, *J. Org. Chem.*, **29**, 4503 (1964).
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(16) P. E. Peterson and J. E. Duddey, *ibid.*, **88**, 4990 (1966).
(17) G. W. Stevenson and D Williamson, *ibid.*, **80**, 5943 (1958).
(18) C. G. Derick, *ibid.*, **33**, 1181 (1911).
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(25) J. C. McGowan, *J. Appl. Chem.*, **10**, 312 (1960).
(26) R. W. Taft, Jr. in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 592.
(27) M. J. S. Dewar, *J. Chem. Soc.*, 463 (1949); 2329 (1950).
(28) H. H. Jaffé, *J. Chem. Phys.*, **21**, 415 (1953).
(29) There is no evidence for anchimeric assistance in the reaction of 1,4-dichlorooctane. In this case there is probably association of the excess hydrogen fluoride with the primary chloro group. In this way the unshaved electrons are not available for participation in the ionization of the secondary chloro group. The behavior of 1,4-dichlorobutane is different because of the presence of only catalytic amounts of aluminum chloride.

Similarly, the same treatment could theoretically be applied to the α,ω-dichloroalkane series. However, the accuracy of the data is not great and provides only a three-point plot. That a linear plot is not obtained cannot be taken as being very meaningful.

Such studies as the one presented here inevitably have a bearing on the controversial question of the mechanism of transfer of the effect of the chloro group. The case for the mechanism being due to a field effect has been presented by Dewar.[30] The arguments for a purely inductive transfer apparently is more acceptable to many chemists.[13-28] The value of the Kirkwood–Westheimer[31] treatment of the first and second dissociation constants of saturated dicarboxylic acids cannot be discounted. Further, more recent investigations have explained long-range effects as field effects[32] or have detected negligible inductive effects for groups separated by more than two carbon atoms.[33,34]

Until a reliable quantitative treatment of field effects has been developed, the dispute will remain. Although long-range effects have been adequately demonstrated in our systems, the mode of transfer of the influence cannot be decided upon on the basis of our work.

Experimental Section

Benzene was stirred thoroughly twice with 5 wt % concentrated sulfuric acid and washed with water, 10% sodium bicarbonate, and water. After partially drying over magnesium sulfate the benzene was refluxed with and then distilled from calcium hydride immediately before use.

1,X-Dichlorooctane.—Into a 1-l. turbomixer, fitted with a gas inlet at the bottom and with a water-cooled condenser, was placed 561 g (3.77 mol) of 1-chlorooctane. Nitrogen was passed through the solution for 15 min and then chlorine was passed at approximately 443 ml/min for 36 min with a sun lamp to cause initiation. After flushing with nitrogen for 30 min, the reaction mixture was washed with water, 10% sodium bicarbonate, water, and dried over magnesium sulfate. The product was distilled through a 9 in. × 1 in. column packed with glass helices; the portion boiling at 112–119° (15 mm) was used in our work.

This material, after distillation, was analyzed on a 200 ft × $^1/_{16}$ in. SF-96 coated capillary column in a Perkin-Elmer 800 chromatograph at 110°. Under these conditions the composition for the 1,1- through 1,8-dichlorooctane, in order, was 2.0, 5.7, 12.2, 16.9, 17.8, 18.6, 20.6, and 4.9%; and the relative retention times in minutes were 9.9, 10.5, 11.4, 12.4, 13.3, 14.2, 14.5, and 18.5, respectively. The product contained 1.2% 1-chlorooctane.

The 1,1, 1,2, 1,4, 1,5, and 1,8 isomers were identified by spiking with authentic materials prepared as follows.

1,1-Dichlorooctane.—The product from the reaction of 1-octanal with phosphorus pentachloride had a 9.9-min retention time.

1,2-Dichlorooctane.—The addition of chlorine to 1-octene with stannic chloride as catalyst gave a product with a 10.5-min retention time.

1,4-Dichlorooctane.—Treatment of γ-octanoic lactone with lithium aluminum hydride yielded a compound which upon treatment with thionyl chloride and pyridine gave a product with a 12.4-min retention time.

1,5-Dichlorooctane.—The hydration of dihydropyran to α-hydroxytetrahydropyran was followed by salting out with potassium carbonate and ether extraction. The dry ether solution, when treated with more than a 2 mol equiv of *n*-propylmagnesium bromide, yielded a compound[35] which, after treatment with thionyl chloride and pyridine, yielded a material with a 13.3-min retention time.

1,8-Dichlorooctane.—Aldrich Chemical Co. 1,8-dichlorooctane had a retention time of 18.5 min.

The products of these reactions and the intermediates gave nuclear magnetic resonance (nmr) spectra consistent with their structures.

Alkylation of Benzene with 1,X-Dichlorooctane.—Into a 1-l. polyethylene bottle fitted with a mechnical stirrer, gas inlet tube, and sampling port was placed 0.2 mol of 1,X-dichlorooctane and 312 g (4 mol) of benzene. The mixture was cooled in ice and 40 ml of liquid hydrogen fluoride added. To the stirred, cooled mixture was added boron trifluoride gas at about 4 ml/min below the surface of the mixture. Samples were taken at various time intervals by pipet after stirring was momentarily interrupted to permit the hydrogen fluoride to settle. Each sample was washed with water, dilute potassium hydroxide, and water and then dried over magnesium sulfate.

Identification of Products from Reaction of 1,X-Dichlorooctane. 7-Phenyl-1-chlorooctane showed nmr[36] bands at 3.32 (t), 2.61 (q), 1.59 (m), and 1.2 (d). Mass spectrum showed parent peak at 224 and a major peak at 105. Infrared showed primary chloride and monosubstituted phenyl.

6-Phenyl-1-chlorooctane showed nmr bands at 3.32 (t), 2.35 (m), 1.59 (m), and 0.76 (t). Mass spectrum showed parent peak at 224, a major peak at 119, and a smaller peak at 195.

4-Phenyl-1-chlorooctane.—The products from the reaction of 1,X-dichlorooctane were treated with 3 wt % aluminum chloride at 0° for 10 min. The 4-phenyl-1-chlorooctane was completely eliminated having been converted with a small amount of the 5-phenyl-1-chlorooctane, into 1-butyltetralin and *cis*- and *trans*-1-propyl-3-methyl tetralin. The ready closure of 4-phenyl-1-chloroalkanes to tetralins has been well established.[2,12] The 6- and 7-phenyl-1-chlorooctanes remained essentially unchanged.

Mass spectral analysis of the mixture showed a parent peak at 224 and peaks at 209 ($-CH_3$), 195 ($-CH_3CH_2$), 181 ($-CH_3CH_2CH_2$), 167 ($-CH_3CH_2CH_2CH_2$), 147 ($-(CH_2)_3Cl$), 133 ($-(CH_2)_4Cl$), 119 ($-(CH_2)_5Cl$), and 105 ($-(CH_2)_6Cl$). This accounts for all major peaks above 100 with exception of one at 159 (not chlorine containing) and a small one at 188 (possibly chlorine containing). In qualitative fashion this analysis bears out the assignments given.

Alkylation of Benzene with α,ω-Dichloroalkanes.—Into a 500-ml, three-necked flask fitted with a stirrer, thermometer, and drying tube was placed 0.3 mol of the dichloride in 300 ml of benzene. The stirrred mixture was cooled in ice; then 2 g (0.015 mol) of aluminum chloride was added in one portion. A mild exotherm ensued, but the over-all reaction temperature was 5 ± 3°. After 2 hr the reaction was terminated by the addition of cold 5% hydrochloric acid. The organic phase was washed with water, dilute sodium bicarbonate, and water before drying over magnesium sulfate.

Analyses were performed on a 10 ft × 0.25 in. 20% Carbowax 20M on Chromosorb W column in an A 350 Aerograph chromatograph. After solvent removal under reduced pressure, larger samples were injected into the column and the major components were trapped and identified by spectroscopic methods.

Product Identification. From 1,3-Dichloropropane.—Product I was identical with the purchased authentic material (Eastman Chemical Co.). Product IV showed nmr[36] bands at 2.42 (t) and 1.85 (q); mass spectral (ms) parent peak at 196; correct infrared (ir) spectrum. Product III and V were identical with products previously reported.[2]

From 1,4-Dichlorobutane.—Product VI showed nmr bands at 3.39 (t), 2.56 (t), and 1.72 (m); ms peak at 168; ir showed monosubstituted phenyl and primary chloride. Product VII showed nmr bands at 3.2 (m), 1.9 (m), and 1.22 (d); ms parent peak at 168, major peak at 105, peak at 153; ir showed monosubstituted phenyl and primary chloride. Product IXa (dodecahydrotriphenylene) showed nmr bands at 2.25 (s) and 1.7 (s); uv 272 mμ; ms parent peak 240; ir identical with that previously reported.[37] Product VIII was identical with authentic material.

(30) (a) M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, **84**, 3539 (1962); (b) M. J. S. Dewar and A. P. Marchand, *ibid.*, **88**, 354 (1966).

(31) J. E. Kirkwood and F. H. Westheimer, *J. Chem. Phys.*, **6**, 506, 513 (1938).

(32) H. D. Holtz and L. M. Stock, *J. Amer. Chem. Soc.*, **86**, 5188 (1964).

(33) H. O. Hooper and P. J. Bray, *J. Chem. Phys.*, **33**, 334 (1960).

(34) H. Spiesecke and W. G. Schneider, *ibid.*, **35**, 731 (1961).

(35) R. Paul, *Bull. Soc. Chim.*, **2**, 311 (1935).

(36) Integrals correct within 5% of that for assigned structure (aromatic peak omitted): s = singlet, d = doublet, t = triplet, q = quarter, and m = multiplet.

(37) "Catalog of Infrared Spectra Data," American Petroleum Institute Research Project-44, Chemical Thermodynamics Center, Texas A & M, College Station, Texas, Serial No. 2267.

From 1,5-Dichloropentane.—Product XII showed nmr bands at 3.33 (t), 2.52 (t), and 2.6 (m); ms parent peak at 182; ir showed monosubstituted phenyl and primary chloride. Product XIII showed nmr bands at 3.32 (t), 2.58 (m), 1.63 (m), and 1.22 (d); ms parent peak at 182, large 105 peak, 167 peak; structure confirmed by ir. Products XIV and XV had ir spectra identical with those previously reported;[9] ms and nmr were consistent. Product XVI showed nmr bands at 2.47 (m), 1.5 (m), and 1.18 (d); ms parent peak at 224, 209 peak; it was consistent.

From 1,6-Dichlorohexane.—Product XVII was identical with purchased material (Ash Stevens Co.). Product XVIII showed nmr bands at 3.3 (t), 2.55 (q), 1.56 (m), and 1.17 (d); ms parent peak at 196, 181 peak; ir showed monosubstituted phenyl. Products XXI, XIX, and XX had ir spectra identical with those previously reported;[10] nmr and ms were consistent.

Registry No.—Benzene, 71-43-2; 7-phenyl-1-chlorooctane, 15733-57-0; 6-phenyl-1-chlorooctane, 15733-58-1; III, 1081-75-0; VI, 4830-93-7; VII, 13556-61-1; IXa, 1610-39-5; XII, 15733-63-8; XIII, 15733-64-9; XVI, 6443-80-7; XVIII, 13556-57-5.

Acknowledgment.—We wish to thank Mr. A. E. Straus of these laboratories for his help with the analytical problems related to the 1,X-dichlorooctane work.

II. Solvent Effects in the Alkylation of Benzene with 1-Dodecene and *trans*-6-Dodecene in the Presence of Aluminum Chloride

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1-Dodecene and *trans*-6-dodecene alkylate benzene in the presence of aluminum chloride–hydrogen chloride at 35–37° to give similar isomer distributions of phenyldodecanes. At that temperature the alkylation reaction is accompanied by isomerization of the products to a certain equilibrium distribution that is different from the isomer distribution in the absence of product isomerization. Alkylation at 0° or below suppresses product isomerization and results in an isomer distribution that depends on the position of the double bond in the olefin. Attenuation of aluminum chloride with nitromethane prevents product isomerization even at the reflux temperature of benzene. Alkylation with both olefins in benzene solution in the presence of aluminum chloride–nitromethane results in widely different isomer distributions which approach each other if the alkylation reaction is carried out in nitromethane solution. These results are explained in terms of formation of secondary carbonium ions with relative stabilities and reactivities that are affected by the solvent and the mobility of the negative ion in the ion pair.

Alkylation of aromatic compounds with various alkylating agents in the presence of strong Friedel–Crafts catalysts such as aluminum chloride has long been known to be accompanied by isomerization and transalkylation.[1–5] This is especially important in the investigation of substrate selectivity and orientation of alkyl groups in di- and polyalkylation. The extent of this isomerization and disproportionation, which alters the product distribution, is determined by the severity of the reaction conditions, namely the strength and amount of the catalysts, the temperature, and the time of the reaction. The same question also occurs in the alkylation of benzene with long-chain α olefins where the products initially formed undergo extensive isomerization in the presence of excess aluminum chloride.[6,7] Thus, Nenitzescu has concluded that the Friedel–Crafts alkylation leading to the formation of phenylalkanes is a kinetically controlled reaction, but the subsequent isomerization of phenylalkanes is a thermodynamically controlled reaction leading to the most stable isomer, which is not always identical with the phenylalkane formed from the most stable carbonium ion.[8] The situation is also somewhat complicated by the fact that isomerization of the initial products can be shifted beyond thermodynamic equilibrium by an excess of $BF_3 \cdot HF$ or $AlCl_3 \cdot HCl$ which often results in the formation of only the product whose intermediate complex with the catalyst is the most stable one.[9] Therefore, it is of interest to find out if the phenylalkanes obtained from the alkylation of benzene with a long-chain α olefin such as 1-dodecene in the presence of aluminum chloride come to equilibrium as a result of their isomerization by the strong catalyst, and if this equilibrium distribution differs from the initial isomer distribution obtained in the absence of product isomerization. It is also of interest to find out if the intermediate carbonium ions also come to equilibrium before they attack benzene and if this equilibrium distribution differs from the final equilibrium distribution obtained as a result of isomerization of the products themselves.

Results

Since alkylation with aluminum chloride proceeds rapidly only after an incubation period during which the so-called red oil forms,[10] the reaction was run in the presence of a small amount (about 20% of the catalyst) of a catalyst layer from a previous alkylation of the same system. At 35° and using 0.12 mol of the catalyst/mol of the olefin, both 1-dodecene and *trans*-6-dodecene afforded nearly identical isomer distribu-

(1) H. C. Brown and C. R. Smoot, *J. Amer. Chem. Soc.*, **78**, 6255 (1956); H. C. Brown and H. J. Ungk, *ibid.*, **78**, 2182 (1956); H. C. Brown and B. A. Bolto, *ibid.*, **81**, 3320 (1959).

(2) K. L. Nelson, *J. Org. Chem.*, **21**, 145 (1956).

(3) R. H. Allen and D. Yats, *J. Amer. Chem. Soc.*, **83**, 2799 (1961).

(4) D. A. McCaulay in "Friedel-Crafts and Related Reactions," Vol. II, G. Olah, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter 24.

(5) G. A. Olah, S. H. Flood, and M. E. Moffat, *J. Amer. Chem. Soc.*, **86**, 1060 (1964); G. A. Olah, S. J. Kuhn, and S. H. Flood, *ibid.*, **84**, 1688 (1962); G. A. Olah, J. C. Lapierre, and H. Schreier, *J. Org. Chem.*, **31**, 1268 (1966); G. A. Olah and J. A. Olah, *ibid.*, **32**, 1612 (1967).

(6) R. D. Swisher, E. F. Kaelble, and S. K. Liu, *ibid.*, **26**, 4066 (1961).

(7) A. C. Olson, *Ind. Eng. Chem.*, **52**, 833 (1960).

(8) C. D. Nenitzescu, *Rev. Roumaine de Chim.*, **9**, 5 (1964).

(9) D. A. McCaulay and A. P. Lien, *J. Amer. Chem. Soc.*, **74**, 6246 (1952).

(10) K. L. Nelson and H. C. Brown in "Chemistry of Petroleum Hydrocarbons," Vol. III, B. T. Brooks, Ed., Reinhold Publishing Corp., New York, N. Y., 1955, Chapter 56.

tions including about 32% 2-phenyldodecane and 31% 5 and 6 isomers. We define this as a distribution ratio of 32:31. However, a small amount of 2-phenyldecane added along with the olefin showed extensive isomerization to its internal isomers, indicating that the phenyldodecanes could also have isomerized after their formation. Under similar conditions but at 0–5° for 30 min, the 2-phenyldecane tracer remained unchanged indicating the absence of any product isomerization as well.[11] The α-olefin product under these conditions had a significantly higher distribution ratio, 44:20, while the internal olefin was very much lower, 18:53. However, when stirring was continued for an additional hour at the same temperature, isomerization appeared in both the 2-phenyldecane and the product phenyldodecanes and was essentially complete after another hour. Further lowering of the temperature (to −15°) completely prevented product isomerization even after several hours of stirring.[12] In spite of the low temperature, alkylation was essentially complete within a few minutes, as evidenced by the absence of the olefin in the glpc analysis of the mixture, but nevertheless extensive isomerization occurred at earlier stages in the reaction since all of the secondary phenyldodecanes were formed.

Product isomerization was also prevented at the higher temperature (35–37°) by alkylation with a recycled catalyst phase instead of fresh $AlCl_3 \cdot HCl$. This also resulted in widely different distribution ratios for 1-dodecene and *trans*-6-dodecene (42:25 and 26:43, respectively) indicating that the isomer distribution of the product depends on the position of the double bond in the starting olefin.

The alkylation reaction was also accompanied by the formation of some C_{12} paraffins which were isolated by distillation and analyzed by mass spectroscopy and gas–liquid partition chromatography. Their amount and type were found to depend on the temperature of the reaction. Thus at 0° only a 2% yield of dodecanes was obtained of which 67% was *n*-dodecane and 33% branched isomers. At 35° a 6% yield of the paraffin was obtained of which only 5.5% was *n*-dodecane and 94.5% was branched.[13] The greater formation of paraffins at the higher temperature resulted in a slight decrease in the yield of the product alkylbenzenes (83 *vs.* 87%). In addition to the paraffins, the reaction was also accompanied by the formation of a small amount of an unsaturated material (3.6%) whose analysis by mass spectroscopy showed it to have the molecular formula C_nH_{2n-8}.

Attenuation of aluminum chloride with nitromethane[14] also prevented product isomerization both in benzene and in nitromethane solutions. Even at the reflux temperature of benzene, no evidence for the isomerization of the secondary alkylbenzenes could be observed. This resulted in the same type of isomer distribution as was obtained from alkylation with aluminum chloride at low temperatures, or with a recycled catalyst phase at 35°, where the position of the double bond was a factor in the isomer distribution of the product. The results of all these alkylations are recorded in Table I where it is seen that in benzene solution and in the absence of any product isomerization the α olefin invariably afforded greater amounts of the 2 isomer (distribution ratio 44:20) while the internal olefin afforded greater amounts of the 5 and 6 isomers (distribution ratio 18:53). This difference in the behavior of the two olefins due to the position of the double bond was largely eliminated by alkylating in the presence of excess nitromethane where both reactants were present in solution in nitromethane (7:1). Under these conditions both olefins afforded almost identical distribution ratios (approximately 27:35) which were significantly different from the 32:31 ratio obtained from alkylation with aluminum chloride under conditions of product isomerization.

Alkylation with aluminum chloride–nitromethane in benzene solution was not accompanied by paraffin formation as was the case with aluminum chloride. The absence of paraffins, however, was not accompanied by a corresponding rise in the yield of alkylbenzenes. Instead, a small decrease was observed (78%) owing to a greater formation of a high-boiling material whose infrared analysis showed it to be primarily *p*- and *m*-dialkylbenzenes (12.1 and 12.65 μ, respectively) in the ratio of 5:1. The yield of the product was further reduced (68%) by alkylation in nitromethane solution owing to the smaller concentration of benzene.

Discussion

It is evident from the above experimental facts that alkylation of benzene with any long-chain olefin in the presence of aluminum chloride at 35° or higher produces the same isomer distribution regardless of the position of the double bond in the original olefin. This is, however, the result of the rapid and efficient isomerization of the products themselves rather than the intermediate carbonium ions coming to equilibrium. Thus at 0° or below, and in the absence of any product isomerization, 1-dodecene and *trans*-6-dodecene give widely different isomer distributions depending on the position of the double bond in the chain. This is similar to alkylation with anhydrous hydrogen fluoride in the absence of *n*-hexane where the alkylation reaction appeared to be too fast to permit the intermediate carbonium ions to come to equilibrium. One major difference from HF alkylations is that addition of *n*-hexane at 0 or 35° made no difference in the isomer distribution of the product, indicating that the reaction takes place exclusively in the catalyst phase. Consequently, the intermediate carbonium ions could not be brought to equilibrium by this method.[15]

Alkylation with $AlCl_3 \cdot CH_3NO_2$ produces essentially the same results as alkylation with aluminum chloride at lower temperatures in that the products under these conditions do not undergo any isomerization[16] and, therefore, they reflect the concentration of the secondary carbonium ions prior to alkylation. Consequently, the isomer distribution of the final product depends on

(11) Product isomerization can also be suppressed by use of smaller amounts of aluminum chloride.[6]

(12) Normal hexane was added to the reaction mixture to prevent the benzene from freezing.

(13) Reduction of the alkylating agent to paraffin has also been observed in the alkylation of benzene with decyl, dodecyl, and hexadecyl chloride in the presence of aluminum chloride at 70°: T. Mazonski and A. Hopfinger, *Przemysl Chem.*, **40**, 453 (1961); *Chem. Abstr.*, **62**, 3957*f* (1965).

(14) L. Schmerling, *Ind. Eng. Chem.*, **40**, 2072 (1948).

(15) H. R. Alul and G. J. McEwan, *J. Org. Chem.*, **32**, 3365 (1967).

(16) Aluminum chloride–nitromethane is also incapable of effecting isomerization of cymenes: G. A. Olah, S. H. Flood, S. J. Kuhn, M. E. Moffat, and N. E. Overchuck, *J. Amer. Chem. Soc.*, **86**, 1046 (1964).

TABLE I

Amount, mol											
1-Dodecene	*trans*-6-dodecene	2-Phenyldecane	Benzene	Nitromethane	$AlCl_3$[a]	Temp, °C	Total time, min	2-Phenyl	3-Phenyl	4-Phenyl	5-, 6-Phenyl
0.3			3.0		0.037	35–37	45	31.8	20.8	17.2	30.2
	0.15	0.01	3.0		0.02	35–37	45	31.9	18.5	17.6	32.0
								38.5[b]	22.0	19.5	20.0[c]
0.3		0.01	3.0		0.037	0–5	30	44.0	22.1	14.2	19.7
								100.0[b]	...	...	...
							90	36.9	20.9	16.8	25.4
								55.8[b]	16.8	15.7	11.7
							150	31.0	20.6	18.9	29.5
								39.5[b]	21.4	22.8	16.3
	0.15	0.01	3.0		0.02	0–5	30	18.1	12.3	16.9	52.7
								100.0[b]	...	...	...
0.3		0.01	3.0		0.037	−15[d]	360	43.0	21.9	14.5	20.6
								100.0[b]	...	...	...
0.3		0.01	3.0		0.037[e]	35–37	30	41.7	19.8	13.2	25.3
								100.0[b]	...	...	...
	0.15	0.01	3.0		0.037[e]	35–37	30	26.0	15.4	15.6	43.0
								100.0[b]	...	...	...
0.15			3.0	0.08[f]	0.037	35–37	60	40.9	20.7	14.4	24.0
0.15		0.01	3.0	0.08[f]	0.037	65	90	42.9	19.1	15.0	23.0
								100.0[b]	...	...	...
						78	60	41.8	20.6	14.7	22.9
								100.0[b]	...	...	...
	0.15	0.01	3.0	0.08[f]	0.037	35–37	60	23.2	17.3	17.8	41.3
								100.0[b]	...	...	...
0.15		0.01	0.5	4.0[e]	0.037	35–37	60	27.9	19.5	18.6	34.0
								100.0[b]	...	...	...
	0.15		0.5	4.0[e]	0.037	35–37	60	26.1	18.3	19.1	36.5
0.15			3.0		0.074[g]	35–37	120	57.0	21.5	9.0	12.5

[a] In addition, 20% by weight of red oil from a previous alkylation of the same system was added. [b] Analysis of the added 2-phenyldecane to detect product isomerization. [c] Amount of the 5 isomer only since the 6 isomer is not possible with the phenyldecanes. [d] *n*-Hexane was added to prevent the benzene from freezing. [e] Only a recycled catalyst phase from a previous alkylation of the same system was used in this experiment. [f] No red oil was added when nitromethane was used. [g] The catalyst used in this experiment was $AlCl_2 \cdot HSO_4$.

the position of the double bond in the chain and, therefore, on the point at which the proton enters the alkylating agent. The condition of equilibrium among the carbonium ions is almost achieved by alkylating in nitromethane solution where the alkylation reaction is sufficiently slowed down to permit greater isomerization in the alkylating agent. However, complete equilibrium in nitromethane was apparently not quite achieved and 1-dodecene continued to give slightly greater amounts of the 2 isomer than *trans*-6-dodecene (27.9 *vs.* 26.1%) and slightly smaller amounts of the 5 and 6 isomers (34.0 *vs.* 36.5%). This is in contrast to the effect of *n*-hexane on alkylations with hydrogen fluoride where complete equilibrium was readily achieved resulting in the same isomer distribution regardless of the point at which the proton enters the chain.[15] This is probably due to the solvation of the intermediate ions by the polar solvent, nitromethane, which affects their relative stabilities and their rates of isomerization across the chain.

The product from alkylation with both olefins at or near equilibrium conditions in nitromethane solution shows about the same amount for all the isomers except the 2-phenyl isomer which is invariably greater than the 3 isomer. At lower temperatures the inherent stability of the 5 and 6 isomers (which was also observed in hydrogen fluoride alkylations) becomes more magnified, and their amount rises to 52.7%.[15] Still, however, the amount of the 2 isomer is greater than the 3 isomer which probably indicates that the 2-carbonium ion reacts with benzene more rapidly than the 3-carbonium ion. The excess of the 2 isomer over the 3 isomer was also observed in some hydrogen fluoride alkylations, but it disappeared upon lowering the polarity of the medium by addition of *n*-hexane.[15] Apparently solvation of the intemediates by a polar solvent such as benzene or nitromethane reduces the differences in their stabilities and concentrations which permits greater formation of the 2-phenylalkane. Removal of this stabilization by addition of *n*-hexane magnifies the differences in these stabilities which raises the concentrations of the internal isomers sufficiently to nullify the steric advantages of the 2 isomer.

The excess of the 2 isomer over the internal phenylalkanes also occurs under conditions of product isomerization such as aluminum chloride–hydrogen chloride and benzene at 35–37°. Under these conditions the phenyldodecanes are at equilibrium as evidenced by the fact that both 1-dodecene and *trans*-6-dodecene afford the same isomer distribution as the equilibrium distribution reported by Swisher, *et al.*[6] The amount of 2-phenylalkane at equilibrium is twice the amount of the 5 or 6 isomers and 50% greater than the 3 isomer. This is probably due to greater solvation of the intermediate alkylarenonium ion by the extremely polar phase (the red oil) of the reaction mixture. In the alkylbenzenonium ion derived from the 2-phenylalkane, the positive charge of the ion is located near the end of the chain which permits more efficient solvation by the catalyst phase. As the charge enters the middle of the chain, the ion is more efficiently shielded from the solvent by its alkyl groups. Therefore, alkylation of

benzene with 1-dodecene results in greater amounts of the 2-phenylalkane both in the absence as well as presence of product isomerization. In the first case, it is due to greater reactivity of the intermediate carbonium ion toward benzene, and in the second case, it is due to greater solvation of the intermediate alkylarenonium ion by the catalyst phase.

Although the isomer distribution of the primary product obtained with $AlCl_3 \cdot HCl$ at 35° is altered by the concurrent isomerization of the phenylalkanes, it appears that the intermediate carbonium ions do not come to equilibrium prior to their reaction with benzene at that temperature. Thus, when a recycled catalyst phase is used instead of fresh aluminum chloride, product isomerization is prevented and the two olefins, 1-dodecene and *trans*-6-dodecene, no longer afford the same isomer distribution.

Comparison of the product from alkylation in the presence of hydrogen fluoride with those from alkylation in the presence of aluminum chloride at 0° shows the first to be closer to equilibrium conditions.[15] Thus 1-dodecene and *trans*-6-dodecene afford 18.5 and 10.6%, respectively, of the 2 isomer in the presence of hydogen fluoride and 44.0 and 18.1%, respectively, in the presence of aluminum chloride. This is probably due to the effect of the negative ion of the ion pair on the rate of isomerization of the positive ion across the chain.[17] This effect of the mobility of the negative ion on the rate of isomerization was also observed by alkylation of benzene with 1-dodecene in the presence of $AlCl_2 \cdot HSO_4$ which resulted in the highest distribution ratio obtained in this series of alkylations (57:13).[18] Further work on this point is in progress in this laboratory.

Since intermolecular hydride abstractions occur more readily with stronger acids such as aluminum chloride–hydrogen chloride,[19] one may also expect them to occur more readily in intramolecular abstractions where the carbonium ion abstracts a hydride from a carbon atom at some distance from the positive charge which, if it occurs to any significant degree, woud result in greater isomerization. The fact that greater isomerization occurs at 0° with 1-dodecene and hydrogen fluoride than with aluminum chloride argues against such long-range isomerization occurring to a significant degree. In any event the rate of isomerization of the intermediate cations is not sufficient to bring them to equilibrium under ordinary conditions.

The formation of the paraffins occurs under conditions which permit disproportionation and *trans*-alkylation. Evidence has been obtained to show that it occurs after the formation of alkylbenzene.[20] This is in accord with the fact that the alkylation reaction is much faster than hydride abstraction[21] so that almost all the carbonium ions are converted into alkylbenzene. At higher temperatures and in the presence of the strong acid aluminum chloride–hydrogen chloride the product is converted to the alkylarenonium ion (I) which may equilibrate with a localized π complex (II)[10,22-24] or dissociate to an alkyl cation (III) and benzene. The π complex isomerizes to the other π complexes,[25] which rearrange to the σ complexes and finally lose a proton to form the rearranged phenylalkanes.[6] The alkyl cations (III) also isomerize by rapid hydride shifts and either realkylate benzene or, to a much smaller extent, abstract the tertiary hydrogen of a molecule of alkylbenzene. The new phenylalkyl cation (IV) rearranges to VI by way of a phenonium-type intermediate[26] (V) which then either abstracts another hydride to form the rearranged alkylbenzene or alkylates benzene to form a high-boiling product. These reactions are summarized in Chart I written for the 2-phenyldodecane isomer.

Some of the alkyl cations (III) undergo skeletal isomerization in a manner similar to that reported by Peterson, *et al.*,[27] and subsequently appear as isoparaffins. The failure to observe *t*-alkylbenzene in the gas–liquid chromatogram is due to its vulnerability to attack by the strong acid.[28] Under the influence of $AlCl_3$–HCl the alkyl cations (III) may abstract a hydride ion from a carbon atom of an alkylbenzene molecule other than the benzylic one.[19] This is more likely to occur with the internal phenyldodecanes where the tertiary hydrogen atom is surrounded by two large alkyl groups. The new phenylalkyl cation undergoes isomerization and then cyclization to form the indanes and tetralines (C_nH_{2n-8}) which have frequently been observed[29,30] or postulated[20] as by-products of these reactions.

Experimental Section

Materials.—1-Dodecene, *trans*-6-dodecene, and benzene were obtained as described previously.[15] Aluminum chloride was Fisher reagent grade and nitromethane was obtained from Eastman Organic Chemicals. 2-Phenyldecane was obtained from Dr. R. D. Swisher of the Monsanto Co.

Alkylation with Aluminum Chloride.—The alkylation reaction was carried out at 35–37° by adding 0.3 mol of 1-dodecene to 3.0 mol of dry benzene which had previously been saturated with dry hydrogen chloride and mixed with 0.037 mol of an-

(17) From the point of view of their catalytic activity in these reactions the most important differences between HF and $AlCl_3 \cdot HCl$ are (a) the difference in their acidity and (b) the difference in the mobility of F^- and $AlCl_4^-$ ions. The Hammett acidity function, H_0, for anhydrous HF is -10 and that for $AlCl_3 \cdot HCl$ is about -15, which makes the latter a much stronger acid. The acidity of hydrogen fluoride, however, can be varied over a very wide range (6 powers of 10) by addition of certain Lewis acids such as BF_3, NbF_5, or SbF_5 which raise the acidity of the solvent. Also the addition of certain salts such as NaF or KF lowers its acidity. This property of hydrogen fluoride solutions permits the study of the effect, if any, of the acidity of the medium on the isomerization of the positive charge across the chain of the secondary carbonium ion. Experiments with various catalyst systems such as HF–BF_3, HF–KF, and HF–KBF_4 failed to show any relation between the acid strength of the catalyst and the isomer distribution of the product if the reaction is carried out under conditions which do not permit product isomerization. The results of this work will be reported in the near future.

(18) It is interesting to note that *n*-propyl chloride has been reported to alkylate benzene in the presence of dichloroaluminum sulfate with no isomerization of the *n*-propyl group: A. V. Topchiev, B. A. Krentsel, and L. N. Andreen, *Dokl. Akad. Nauk SSSR*, **92**, 781 (1953); *Chem. Abstr.*, **49**, 3039 (1955). Subsequent work on the alkylation of benzene with 8-methyl-1-nonene showed that under these conditions of minimum isomerization the positive charge barely reaches the eighth carbon atom of the chain, while under conditions of maximum isomerization[15] it winds up almost exclusively on it. The result of this work will be reported in a future communication.

(19) H. Pines and N. E. Hoffman, ref 4, Chapter 28, p 1215.

(20) A. Metzger and C. Uhlig, *Tenside*, **3**, 6 (1966).

(21) F. E. Condon and M. P. Mutuszak, *J. Amer. Chem. Soc.*, **70**, 2539 (1948).

(22) H. C. Brown and H. Jungk, *ibid.*, **77**, 5579 (1955); H. C. Brown and C. R. Smoot, *ibid.*, **78**, 2176 (1956).

(23) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **I**, 42, (1963).

(24) G. Olah and N. Overchuck, *J. Amer. Chem. Soc.*, **87**, 5786 (1965).

(25) A. Streitwieser, Jr., W. D. Schaeffer, and S. Andreades, *ibid.*, **81**, 1115 (1959).

(26) Reference 4, p 1065.

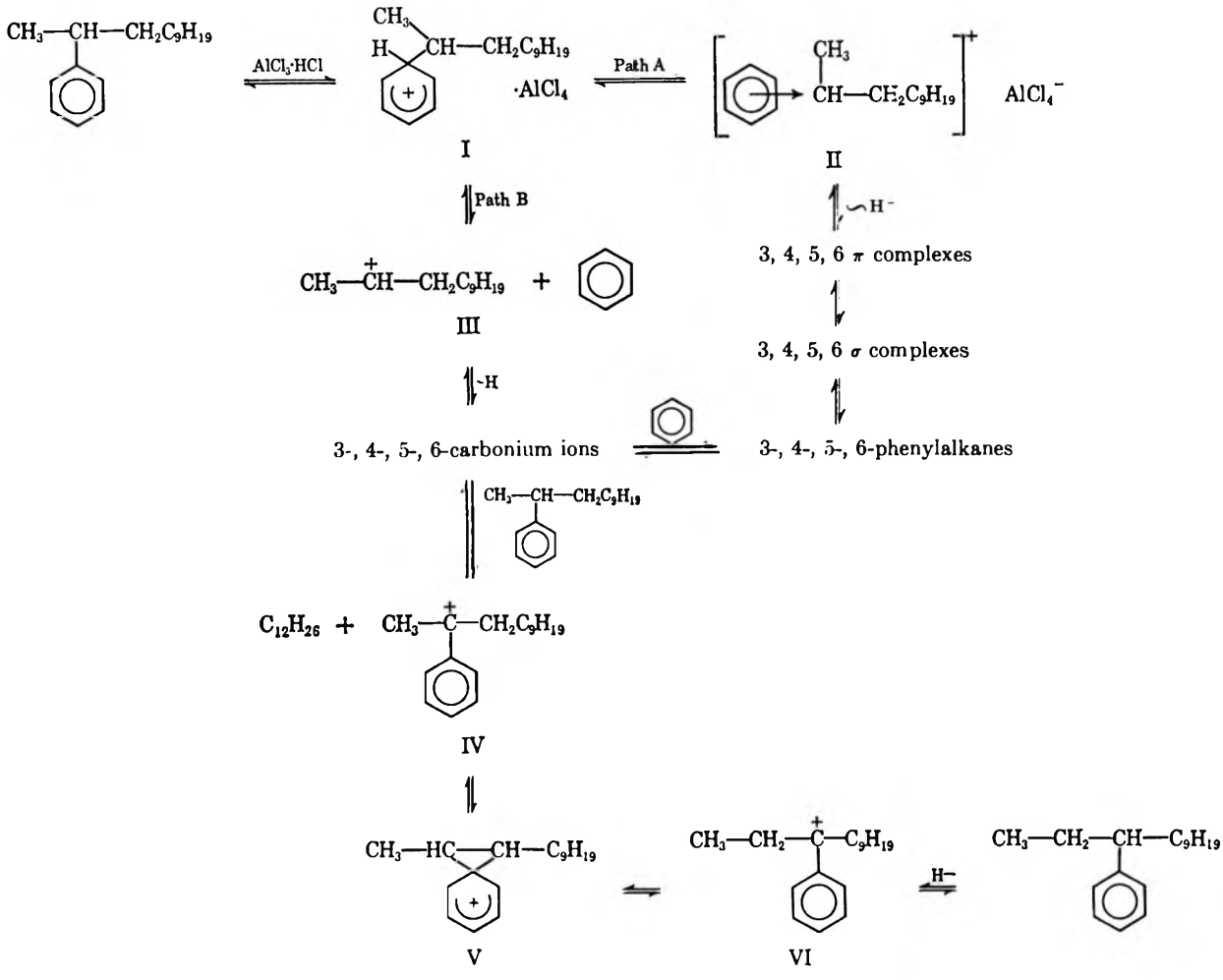
(27) A. H. Peterson, B. L. Philips, and J. J. Kelly, *Ind. Eng. Chem.*, **4**, 261 (1965).

(28) F. A. Drahowzal, ref 4, Chapter 17, p 448.

(29) P. W. Flanagan, M. C. Hamming, and F. M. Evans, *J. Amer. Oil Chemists' Soc.*, **44**, 30 (1967).

(30) A. A. Khalaf and R. M. Roberts, *J. Org. Chem.*, **31**, 89 (1966).

CHART I



hydrous aluminum chloride and about 1 ml of a red oil from a previous alkylation. After separation of the catalyst complex phase from the alkylated liquor, the latter was quenched by adding water, washed with 5% NaOH solution followed by water, and dried. A small sample was analyzed by gas–liquid chromatography using a Barber–Colman Model 20 chromatograph equipped with Sargent SR recorder with a coupled integrator. The column used for the analysis was 150 ft × 0.02 in. stainless steel coated with SE-30 silicon gum rubber. Another column of the same dimensions but coated with *m*-bis[*m*-(*m*-phenoxyphenoxy)phenoxy]benzene[31] was also used. The excess benzene was removed on a water bath, and the rest of the mixture was distilled in a 2-ft packed column under vacuum. After a small amount of benzene (n^{25}D 1.4930) had been removed, the first fraction boiled at 85–115° (15 mm), n^{25}D 1.4335 (2.8 g or 6%). It was passed through a column of silica gel to remove any unsaturated impurities and then examined by glpc rapid scan mass spectrometry. The spectrometer used was Consolidated Electrodynamics Corp. (CEC) conventional mass spectrometer, model 21-130, modified for rapid scanning. The glpc separation was made on a 200 ft × 0.02 in. d capillary column coated with 10% didecyl phthalate (DDP). Six major peaks appeared and accounted for about 95% of the entire chromatogram. The boiling points of the various components were computed from their retention times and were found to lie between 205 and 215° (*n*-dodecane bp 215°). The effluent from the glpc column was passed through the continuous capillary inlet of the mass spectrometer where each of the six peaks was found to be a paraffin with the molecular formula $C_{12}H_{26}$. The last peak (5.5% of the chromatogram) showed a fragmentation pattern similar to published data.[32] It had a parent peak (P) at *m/e* 170 ($C_{12}H_{26}$) in addition to groups of peaks differing by 14 (CH_2) mass units. The peak at *m/e* 155 (P − CH_3) was absent, which is characteristic of straight-chain paraffins.[33] The identification of this component as *n*-dodecane was further supported by the use of an authentic sample of the straight-chain paraffin. The other five components which eluted before *n*-dodecane also showed parent peaks of *n*-dodecane, as well as a strong peak at *m/e* 155 (P − CH_3). Some of the components showed prominent peaks at even mass numbers (142, 126, 112, 98) which is characteristic of two side chains and a higher degree of branching.[33] These branched dodecanes, however, could not be assigned individual structures due to the lack of model compounds. The same result was confirmed by simple glpc analysis using an 18 ft × 0.25 in. id column packed with Carbowax–silver nitrate. The *n*-dodecane peak was well resolved and was identified by use of an authentic sample. The other peaks eluted before the *n*-dodecane but were less well resolved.

The main fraction of the product boiled at 128–136° (2 mm) (n^{25}D 1.4807), and the yield was 62 g or 83% of theoretical. A sample of the product was analyzed by conventional mass spectrometry using the major ion fragments to represent various isomer species, *i.e.*, *m/e* 105 (2-phenyl), 119 (3-phenyl), 133 (4-phenyl), 147 (5-phenyl), and 161 (6-phenyl).[34] The parent molecular ion peak (P) for all the above isomers was observed at *m/e* 246. The spectrum also contained a small amount (3.6%) of a component whose P appeared at *m/e* 244 (C_nH_{2n-8}).[20,29,30]

When the reaction was carried out at 0°, small samples from the reaction mixture were withdrawn at definite intervals, quenched with water, washed with 5% sodium hydroxide solution and water, and finally analyzed by gas–liquid partition chromatography for the isomer distribution of both the phenyldecanes, present to detect product isomerization, and the product phenyldodecanes. The column, SE-30 silicon gum rubber, and the procedure were as above. The yield of this reaction was 87% of

(31) Commonly known as poly-*m*-phenyl ether (seven-ring) and obtained from Monsanto Research Corp., Dayton, Ohio.

(32) "Mass Spectral Data," American Petroleum Institute Research Project No. 44; Spectral No. 404, 981, 1028, 1598.

(33) J. H. Beynon, "Mass Spectrometry and Its Applican to Organic Chemistry," Elsevier, Amsterdam, 1960, p 329.

(34) Reference 32, Spectral No. 1743–1747.

theoretical. At temperatures below 0° about 100 ml of *n*-hexane was added to prevent the benzene from freezing.[35]

The same procedure was followed for the alkylation of benzene with *trans*-6-dodecene. The olefin (0.15 mol) was mixed with 0.01 mol of 2-phenyldecane, and the alkylation reaction was completed as above. The mixture was worked up as usual and the analysis of the product appears in Table I. The yields were similar to those obtained with 1-dodecene.

Alkylation in the Presence of Aluminum Chloride–Nitromethane.—Benzene (2.5 mol) was added to the yellowish solution prepared by dissolving 0.037 mol of anhydrous aluminum chloride in 0.08 mol of nitromethane. The temperature was kept at 35–37°, and a mixture of 0.15 mol of 1-dodecene and 0.01 mol of 2-phenyldecane in 0.5 mol of benzene was added over a period of 15 min. The mixture was stirred for 45 more minutes and was quenched with water and washed with dilute HCl, 10% NaOH solution, and water. The product was analyzed by glpc and distilled as usual. The yield was 28.5 g or 78%. Infrared analysis of the residue (7.3 g) showed it to be mainly *p*- and *m*-dialkylbenzene in the ratio of 5:1 (12.1 and 12.65 μ, respectively).

The same procedure was followed for the alkylation reactions in nitromethane solution. A mixture of 0.15 mol of 1-dodecene, 0.01 mol of 2-phenyldecane, and 0.1 mol of benzene was added to a solution of 0.037 mol of anhydrous aluminum chloride in 4.0 mol of nitromethane and 0.4 mol of benzene maintained at 35–37°. Stirring was continued for 1 hr, and the reaction mixture was quenched with 10 g of ice and extracted three times with 200 ml of *n*-hexane. The combined hexane extracts were washed with dilute hydrochloric acid, water, 10% sodium hydroxide solution, and finally water. The solution was dried with anhydrous magnesium sulfate, and the solvent was removed on a water bath. The product was analyzed for isomer distribution and then distilled as above. The yield was 68% of theoretical.

Alkylation with Dichloroaluminum Sulfate.—This catalyst was prepared according to the directions of Topchiev, *et al.*[36] Ground $AlCl_2 \cdot HSO_4$ (0.074 mol) and anhydrous benzene (3.0 mol) were placed in the alkylation flask. The temperature was raised to 35°, and a mixture of 0.15 mol of 1-dodecene and 0.01 mol of 2-phenyldecane was added. Stirring was continued for 2 hr after which time an oily layer appeared at the bottom of the flask. The mixture was allowed to stand overnight before it was quenched with water and acidified with dilute HCl. The organic layer was washed successively with dilute HCl, water, dilute alkali, and finally water. The product was then analyzed by glpc and distilled as usual. The yield was 27.5 g or 75%.

Registry No.—Benzene, 71-43-2; 1-dodecene, 112-41-4; *trans*-6-dodecene, 7206-17-9; aluminum chloride, 7446-70-0.

Acknowledgment.—Mr. Minor T. Jackson and Mr. Donald A. Wallace of the Central Research Department of the Monsanto Co. carried out the mass spectral analysis.

(35) Special alkylations were carried out at 0 and 35° in which n-hexane, in contrast to hydrogen fluoride alkylations, was shown to have no effect on the isomer distribution of the product.

(36) A. V. Topchiev, S. V. Zavgorodnii, and V. G. Kryuchkova, "Alkylation with Olefins," Elsevier Publishing Co., Amsterdam, 1964, p 141.

The Synthesis and Properties of 1- and 2-(Dichloromethyl)heptamethyltrisilane and Related Compounds[1]

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The first carbon-functional organotrisilanes, 1- and 2-(dichloromethyl)heptamethyltrisilane, have been prepared from the corresponding chloroheptamethyltrisilanes with α-dichloromethyllithium. 1-(Chloromethyl)-heptamethyltrisilane as well as (chloromethyl)pentamethyldisilane were also prepared by *in situ* coupling of bromochloromethane with the corresponding chlorosilanes. Aluminum chloride catalyzed reactions of 1- and 2-(dichloromethyl)heptamethyltrisilane were examined. Both compounds undergo intramolecular rearrangement followed by a redistribution reaction. Nmr spectral data are reported for several chloromethyl- and dichloromethyl-substituted silanes.

Recently considerable attention has been directed toward a study of the organopolysilanes.[2] However, no carbon-functional organotrisilane except vinylheptamethyltrisilanes[3] has been known to date. We now report the synthesis and aluminum chloride catalyzed rearrangement of the first examples of the carbon-functional organotrisilanes, 1- and 2-(dichloromethyl)-heptamethyltrisilane.

Many procedures for preparing carbon-functional silanes or disilanes[4] cannot be extended to higher polysilanes because of extensive silicon–silicon bond cleavage. These procedures involve halogenation or other substitution reactions on carbon. Alternatively, nucleophilic substitution reaction on a silicon atom would be a preferred route to the carbon-functional organopolysilanes. The (dichloromethyl)heptamethyltrisilanes were thus prepared by the reaction of the corresponding chloroheptamethyltrisilanes with α-dichloromethyllithium.

Recently the reaction of polychloromethane with *n*-butyllithium in tetrahydrofuran at low temperature has been shown to lead to the formation of a new class of organolithium reagents, the α-chloroalkyllithium compounds.[5] It was reported that the action of *n*-butyllithium on methylene chloride at −65° afforded dichloromethyllithium in high yield and this reagent served as an intermediate in the preparation of some dichloromethyl-substituted compounds.[6]

(1) (a) Aluminum Chloride-Catalyzed Reactions of Organosilicon Compounds. V. (b) For part IV, see H. Sakurai, K. Tominaga, T. Watanabe, and M. Kumada, *Tetrahedron Lett.*, 5493 (1966).

(2) For pertinent reviews, see (a) H. Gilman, W. H. Atwell, and F. K. Cartledge, *Advan. Organometal. Chem.*, **4**, 1 (1966); (b) M. Kumada and K. Tamao, *ibid.*, in press; (c) H. Sakurai, *J. Soc. Org. Syn. Chem. Jap.*, **25**, 555, 642 (1967).

(3) H. Sakurai, K. Tominaga, and M. Kumada, *Bull. Chem. Soc. Jap.*, **39**, 1279 (1966).

(4) C. Eaborn, "Organosilicon Chemistry," Butterworth and Co. Ltd., London, 1960, p 377.

(5) (a) H. Heaney, *Organometal. Chem. Rev.*, **1**, 27 (1966); (b) G. Köbrich, *et al.*, *Angew. Chem.*, **79**, 15 (1967); (c) D. F. Hoeg, D. L. Lusk, and A. L. Crumbliss, *J. Amer. Chem. Soc.*, **87**, 4147 (1967), and references cited therein.

(6) G. Köbrich, K. Flory, and W. Drischel, *Angew. Chem.*, **76**, 536 (1964).

TABLE I
PROPERTIES OF NEW COMPOUNDS

Compound	Bp, °C (mm)	$n^{20}D$	d^{20}_4	MRD Calcd	MRD Found	Calcd, % C	Calcd, % H	Found, % C	Found, % H
$Cl_2CHSi(CH_3)_2Si(CH_3)_2Si(CH_3)_3$	78 (4)	1.4993	0.9858	81.8	81.0	35.14	8.12	35.24	8.25
$(CH_3)_3SiSi(CH_3)(CHCl_2)Si(CH_3)_3$	104–105 (10)	1.5009	0.9946	81.8	80.9	35.14	8.12	34.99	7.92
$ClCH_2Si(CH_3)_2Si(CH_3)_2Si(CH_3)_3$	50 (4)	1.4842	0.8942	77.0	76.8	40.04	9.66	40.30	9.78

(Dichloromethyl)heptamethyltrisilanes together with the known (dichloromethyl)pentamethyldisilane[7] were prepared successfully by the following route.[8]

$$CH_2Cl_2 \xrightarrow[THF]{n\text{-BuLi}} Cl_2CHLi \xrightarrow{RR'(CH_3)SiCl} RR'(CH_3)SiCHCl_2$$

1a, R = $(CH_3)_3SiSi(CH_3)_2$; R′ = CH_3
b, R = R′ = $(CH_3)_3Si$
c, R = $(CH_3)_3Si$; R′ = CH_3

Physical properties of these compounds are listed in Table I.

It has been described in the literature[9] that the chloromethyl-substituted methylsilanes undergo Lewis acid catalyzed rearrangement resulting in migration of a methyl group from silicon to adjacent carbon.

$$(CH_3)_3SiCH_2Cl \xrightarrow{AlCl_3} (CH_3)_2Si(CH_3)CH_2^{+}\ AlCl_2Cl^{-} \rightarrow (CH_3)_2SiClCH_2CH_3$$

An interesting example involving two successive and discrete intramolecular rearrangements of **1c** with anhydrous aluminum chloride has been reported previously from this laboratory.[7]

In the present study, we have also examined an aluminum chloride catalyzed rearrangement of **1a**. It was expected to obtain a rearranged compound like **3** by the following reactions.

$$(CH_3)_3SiSi(CH_3)_2Si(CH_3)_2CHCl_2 \xrightarrow[0°]{AlCl_3}$$
1a

$$(CH_3)_3SiSi(CH_3)_2CHClSi(CH_3)_2Cl \xrightarrow[0–40°]{AlCl_3}$$
2

$$Cl(CH_3)_2SiCH(Si(CH_3)_3)Si(CH_3)_2Cl$$
3

When a catalytic amount of anhydrous aluminum chloride was added to **4a** at about 0°, a vigorous exothermic reaction took place. By raising the reaction temperature to about 40° and employing a larger amount of the catalyst, the second exothermic reaction occurred. The reaction products were isolated by simple distillation from the mixture. However, contrary to our expectation, the reaction product (83.0% yield) was found to be a mixture consisting of four components, two of which were identified as tris(trimethysilyl)methane[10] (**4**) and tris(dimethylclorosilyl)methane[11] (**5**) by comparing retention times of glpc with those of the corresponding authentic samples. This mixture gave **4** as a single product by methylation with methylmagnesium bromide in good yield (86.4%). Determination of the chlorine content of the mixture by alkaline titration indicated that the mixture had two hydrolyzable chlorine atoms in a molecule on an average. These facts suggest that other unidentified components must be bis(trimethylsilyl)dimethylchlorosilylmethane (**6**) and bis(dimethylchlorosilyl)trimethylsilylmethane (**7**).

$$3 \xrightarrow{AlCl_3} [(CH_3)_3Si]_3CH + [Cl(CH_3)_2Si]_3CH +$$
4 **5**

$$[(CH_3)_3Si]_2CHSi(CH_3)_2Cl + [Cl(CH_3)_2Si]_2CHSi(CH_3)_3$$
6 **7**

$$\text{mixture} \xrightarrow{CH_3MgBr} [(CH_3)_3Si]_3CH$$

Accordingly, the rearranged product must undergo aluminum chloride catalyzed redistributions rather readily under the present reaction condition. This unexpected facile redistribution has been confirmed further by an experiment on the aluminum chloride catalyzed redistribution starting from an equimolar mixture of **4** and **5** at 70°. After 9 hr it was disclosed that the mixture was also composed of **4**, **5**, **6**, and **7**.

$$[(CH_3)_3Si]_3CH + [Cl(CH_3)_2Si]_3CH \xrightarrow{AlCl_3} 4 + 5 + 6 + 7$$

Essentially the same results were obtained from the aluminum chloride catalyzed reactions of **1b**; **4** was produced as the final product by methylation.

$$(CH_3)_3SiSi(CH_3)(CHCl_2)Si(CH_3)_3 \xrightarrow[0°]{AlCl_3}$$

$$4 + 5 + 6 + 7 \xrightarrow{CH_3MgBr} [(CH_3)_3Si]_3CH$$

Attempts to isolate an intermediate like **2** has failed because of high reactivity of the intermediate itself toward aluminum chloride (see Experimental Section).

It seems noteworthy that **5** as well as the rearrangement mixtures from **1a** and **1b** are rather inert toward methylmagnesium bromide. Reflux for 20 hr was not sufficient for completing the methylation; additional refluxing (20–30 hr) was required. It seems reasonable that the low reactivity of these compounds might be due to steric crowding of atoms.[12]

Synthetic routes have been also examined which provide a general way to the chloromethyl-substituted polysilanes. (Chloromethyl)pentamethyldisilane was successfully prepared by photochlorination of methyl-

(7) M. Kumada and M. Ishikawa, *J. Organometal. Chem.*, **1**, 411 (1964).
(8) After this manuscript had been completed, we received a paper of W. R. Bamford and B. C. Pant, *J. Chem. Soc., Sect. C*, 1470 (1967), in which (dichloromethyl)trimethylsilane, (trichloromethyl)trimethylsilane, and related compounds have been prepared by the addition of *n*-butyllithium to a mixture of chlorotrimethylsilane and certain chloroalkanes in tetrahydrofuran at −120°.
(9) (a) See ref 4, p 434; (b) R. W. Bott, C. Eaborn, and B. M. Rushton, *J. Organometal. Chem.*, **3**, 455 (1965).
(10) R. L. Merker and M. J. Scott, *J. Amer. Chem. Soc.*, **85**, 2243 (1963), *J. Organometal. Chem.*, **4**, 97 (1965).
(11) See ref 1b.
(12) H. Sakurai, T. Watanabe, and M. Kumada, *J. Organometal. Chem.*, **9**, 11 (1967).

$$(CH_3)_nSi_2Cl_{6-n} \xrightarrow{Cl_2,\ h\nu} (ClCH_2)(CH_3)_{n-1}Si_2Cl_{6-n} \xrightarrow{CH_3MgBr} ClCH_2Si_2(CH_3)_5$$

$n = 3, 4$

chlorodisilanes[13] followed by methylation. However, obviously this method cannot be applied to higher polysilanes.

Methoxymethyl-[14] and thiomethoxymethyl-substituted[15] silanes were prepared by the *in situ* Grignard method from chloromethyl methyl ether and chloromethyl methyl sulfide, respectively. Accordingly, *in situ* Grignard reaction of bromochloromethane with

$$CH_3YCH_2Cl + ClSiR_3 + Mg \longrightarrow CH_3YCH_2SiR_3$$
$$Y = O, S$$

chloropentamethyldisilane was examined but none of the expected compound was formed. Only partial success (16–18% yield) was achieved by the coupling reaction of bromochloromethane and chloropentamethyldisilane with lithium metal. A new carbon-functional organotrisilane, (chloromethyl)heptamethyltrisilane, was prepared in low yield by this method (Table I).

$$BrCH_2Cl + ClSi_2(CH_3)_5 + Li \longrightarrow ClCH_2Si_2(CH_3)_5$$

Nmr spectral data for these new compounds together with previously known chloromethyl- or dichloromethyl-substituted methylsilanes are recorded in Table II.

TABLE II
NUCLEAR MAGNETIC RESONANCE SPECTRA OF CHLOROMETHYL- AND DICHLOROMETHYL-SUBSTITUTED SILANES[a]

Silane (no.)	τ values
$(CH_3)_3SiCH_2Cl$ (1)	9.86 (H^1), 7.30 (H^2)
$(CH_3)_3SiSi(CH_3)_2CH_2Cl$ (2)	9.87 (H^1), 9.84 (H^2), 7.19 (H^3)
$(CH_3)_3SiSi(CH_3)_2Si(CH_3)_2CH_2Cl$[b] (3)	9.88 (H^1), 9.86 (H^2), 9.80 (H^3), 7.17 (H^4)
$(CH_3)_3SiCHCl_2$ (4)	9.73 (H^1), 4.86 (H^2)
$(CH_3)_3SiSi(CH_3)_2CHCl_2$ (5)	9.75 (H^1), 9.67 (H^2), 4.74 (H^3)
$(CH_3)_3SiSi(CH_3)_2Si(CH_3)_2CHCl_2$[b] (6)	9.86 (H^1), 9.80 (H^2), 9.71 (H^3), 4.64 (H^4)
$[(CH_3)_3Si]_2Si(CH_3)CHCl_2$[c] (7)	9.78 (H^1), 9.78 (H^2), 4.57 (H^3)

[a] These spectra were determined in carbon tetrachloride solution with cyclohexane as an internal standard. Chemical shifts are converted to τ values taking 1.43 ppm as the signal differences between cyclohexane and tetramethylsilane. A Jeol JNM-C-60 H nmr spectrometer was employed. [b] Assignments of H^2 and H^3 are tentative. [c] Only two kinds of proton peaks were observed; see ref 3.

Experimental Section

Materials.—Chloropentamethyldisilane and 1-chloroheptamethyltrisilane were prepared from hexamethyldisilane and octamethyltrisilane, respectively, by the procedure described before.[11] 2-Chloroheptamethyltrisilane was prepared from 2-phenylheptamethyltrisilane.[16] Tris(trimethylsilyl)methane[10] and tris(dimethylchlorosilyl)methane[11] were prepared by Watanabe in this laboratory. Trimethylchlorosilane was generously supplied by the Tokyo Shibaura Electric Co. Ltd. Methylene chloride and bromochloromethane were purchased and used after distillation.

Preparation of (Dichloromethyl)pentamethyldisilane.—A mixture of 400 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride), 100 ml of dry ether, and 9.0 g (0.1 mol) of dichloromethane was cooled to −78° and 0.065 mol of *n*-butyllithium in 100 ml of ether was added slowly. After the addition, the mixture was stirred 40 min and 16 g (0.1 mol) of chloropentamethyldisilane was added in one portion. The mixture was kept at −78° for 2 hr with stirring and then allowed to warm up gradually to room temperature. The reaction mixture was distilled under reduced pressure. After fractional distillation through a column packed with glass helicoils, 8 g (0.037 mol, 57% yield) of (dichloromethyl)pentamethyldisilane was obtained as a pure colorless liquid (homogeneous on glpc), bp 75–78° (17 mm). This compound exhibits an identical ir spectrum and the same retention times on glpc as a sample prepared by a different route.[7]

Preparation of 1-(Dichloromethyl)heptamethyltrisilane (1a).—A mixture of 400 ml of dry tetrahydrofuran and 29.5 g of dichloromethane (0.35 mol) was cooled to −78° and 0.08 mol of *n*-butyllithium was added slowly over 60 min. After a total of 100 min elapsed, 14.5 g of 1-chloroheptamethyltrisilane (0.06 mole) dissolved in 10 ml of tetrahydrofuran was added over a 30-min period. After work-up as above, **1a** was obtained as a pure colorless liquid in 35% yield.

Preparation of 2-(Dichloromethyl)heptamethyltrisilane (1b).—Essentially by the same procedure as for **1a**, **1b** was prepared from 2-chloroheptamethyltrisilane in 50% yield.

Reactions of 1a with Anhydrous Aluminum Chloride.—To 8.5 g (0.031 mol) of **1a**, stirred and protected from moisture, was added anhydrous aluminum chloride in small portions with cooling by ice bath. A vigorous, exothermic reaction took place. After a total of about 20 mg of aluminum chloride was added, no further noticeable change accurred at ice-bath temperature with an addition of catalyst. Then an additional 60 mg of catalyst was added and the mixture was warmed gradually. At about 40°, a second exothermic reaction took place vigorously. When the reaction subsided, gentle heat was applied with an additional 450 mg of aluminum chloride. The mixture was stirred at 60–80° for 8 hr and was flash distilled under reduced pressure to separate the products from the catalyst. A crystalline material, bp 53–62° (1 mm), was obtained, yield 7 g (83%). This material consists of four components (on glpc), two of which were identified as tris(trimethylsilyl)methane and tris(dimethylchlorosilyl)methane. The mixture was analyzed by titrating the hydrolyzable chlorine (bonded to silicon atoms) and so estimated to contain 27.23% (weight %) of chlorine. This figure corresponds to 2.1 chlorines in a molecule assuming that the mixture had the same molecular weight on an average as **1a** (273.43). By refluxing with a 0.1-mol solution of methylmagnesium bromide in ether, 6 g (0.022 mol) of the mixture gave after work-up 4.5 g (0.019 mol) of tris(trimethylsilyl)methane, 96–102° (20 mm).

Attempts to Isolate an Intermediate in the Reaction of 1a with Aluminum Chloride.—To 3.8 g of **1a** was added a total of 180 mg of anhydrous aluminum chloride essentially by the same procedure as above except for additional warming. To this mixture, 1 ml of acetone was added to deactivate the catalyst.[17] The mixture was then flash distilled under reduced pressure to give 2 g of the mixed product boiling at 30–45° (4 mm). An examination by glpc disclosed that the mixture was composed of six components, four of which had the same retention times as those of the product from **1a** with aluminum chloride (*vide supra*). Another peak was identified as the starting material. Methylation of the mixture gave 1 g of product, boiling up to 38° (4 mm). It consists mainly of tris(trimethylsilyl)methane with some higher boiling products. The ir spectra of this mixture exhibited bands at 1040 and 800 cm^{-1} in addition to those observed for tris(trimethylsilyl)methane. These observations suggest the existence of an intermediate such as $(CH_3)_3SiCHClSi(CH_3)_2Si(CH_3)_3$ (after methylation); however, no further attempt to isolate the compound was made because of an extensive decompositon on gas chromatographic separation.

Reaction of 1b with Anhydrous Aluminum Chloride.—2-(Dichloromethyl)heptamethyltrisilane (2.5 g, 0.01 mol) was subjected to the reaction with 100 mg of anhydrous aluminum chloride essentially by the same procedure to give 1.5 g of a mix-

(13) M. Kumada, J. Nakajima, M. Ishikawa, and Y. Yamamoto, *J. Org. Chem.*, **23**, 292 (1958).
(14) M. Kumada, M. Ishikawa, and K. Tamao, *J. Organometal. Chem.*, **5**, 226 (1966).
(15) H. Sakurai, M. Kira, and M. Kumada, *Chem. Commun.*, 889 (1967).
(16) M. Kumada, M. Ishikawa, and S. Maeda, *J. Organometal. Chem.*, **2**, 478 (1964).
(17) H. Sakurai, K. Tominaga, and M. Kumada, *Bull. Chem. Soc. Jap.*, **39**, 1820 (1966).

ture boiling at 65–72° (2.5 mm). The mixture exhibited a gas chromatogram almost identical with that for the reaction product of **1a**, with slight differences in relative peak areas. The mixture gave tris(trimethylsilyl)methane with a small amount of an unidentified compound by methylation. The latter compound had OH absorption at 3400 cm^{-1} (silanol), being presumably $((CH_3)_3Si)_2CHSi(CH_3)_2OH$.

Aluminum Chloride Catalyzed Redistribution between 4 and 5.—In a 50-ml three-necked flask fitted with an air-tight stirrer, a calcium chloride tube, and a stopper, 2 g (0.0095 mol) of **4**, 2.5 g (0.0095 mol) of **5**, and 0.3 g of freshly sublimed aluminum were placed. The mixture was heated at 70–80° for 9 hr and was flash distilled to give 2.5 g of crystalline materials boiling at 70–115° (24 mm). The product was found to consist only of the same four components as those of the reaction mixture from **1a** or **1b**. The relative peak area of **4**:6:**7**:**5** (on silicone DC 550) was 1:9.3:11:2.4.

Preparation of (Chloromethyl)pentamethyldisilane.—To 3.0 g (0.43 g-atom) of dispersed lithium metal in 100 ml of dry ether was added 33 g (0.2 mol) of chloropentamethyldisilane in one portion at 0° under a nitrogen stream and then 25 g (0.19 mol) of bromochloromethane was added over a period of 30 min. After the addition was complete, the mixture was stirred for 2 hr at 0°. The mixture was then kept at room temperature overnight and hydrolyzed with saturated ammonium chloride solution. After work-up, the mixture was fractionated to give 6 g (18%) of (chloromethyl)pentamethyldisilane, 12 g of bis(pentamethyldisilanyl) ether, and 7 ml of mixture containing bis(pentamethyldisilanyl)methane, decamethyltetrasilane, and other unidentified materials. The (chloromethyl)pentamethyldisilane thus obtained was identified by comparing its ir spectrum and gas chromatogram with those of authentic sample.

Preparation of 1-(Chloromethyl)heptamethyltrisilane.—By the same procedure as above, 12 g of a mixture containing mainly 1-(chloromethyl)heptamethyltrisilane was obtained from 2 g (0.28 g-atom) of lithium, 15 g (0.066 mol) of 1-chloroheptamethyltrisilane, and 40 g (0.3 mol) of bromochloromethane. Pure 1-(chloromethyl)heptamethyltrisilane was isolated from the mixture by preparative glpc.

Registry No.—1, 2344-80-1; 2, 5181-46-4; 3, 15816-06-5; 4, 5926-38-5; 5, 15816-03-2; 6, 15816-04-3; 7, 15816-05-4.

The Reactions of Trichloroacetyl Chloride with 2-Picoline N-Oxide and Pyridylcarbinols

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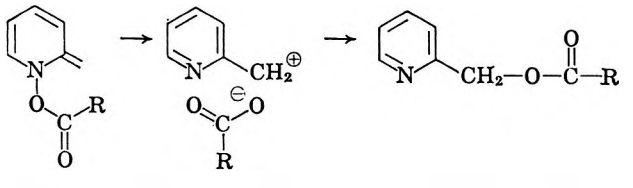
The reaction of trichloroacetyl chloride with 2-picoline N-oxide gives 2-pyridylmethyl chloride and carbon dioxide in high yields. This is shown to be a result of a reaction of the expected trichloroacetate ester with chloride ion. The formation of pyridyl chlorides from trichloroacetyl chloride and the corresponding alcohols is a general reaction.

The concerted decompositions of the *t*-butyl per esters of acids such as pivalic,[2,3] phenylacetic,[2-4] and trichloroacetic[2] seem to be well-established processes. If such behavior is general for any X–O bond homolysis, then the incorporation of such a structural feature into an acyloxy side chain should serve as a useful method for making the difficult choice between intramolecular radical-pair and ion-pair reactions. When the radical path is operative, nearly quantitative amounts of carbon dioxide should be obtained no matter how efficient the cage combination, which might explain the normal products, is proposed to be.

We have recently[5] applied this criterion to the cleavage of the –N–O– bond in the rearrangement of the anhydro bases thought to be involved in the reaction



of 2-picoline N-oxide with acid anhydrides. The results of this study indicated that this cleavage was ionic since the carbon dioxide yields were not significantly increased on going from acetic to phenylacetic or trichloroacetic anhydride as reagent. During the course of these investigations we also examined the reaction of 2-picoline N-oxide with trichloroacetyl chloride. This reaction gave the qualitatively conflicting result that carbon dioxide is produced in high yield at a fairly rapid rate. We now wish to report the results of further studies of this reaction which indicate that trichloroacetate esters are susceptible to displacement by chloride ion under these relatively mild conditions.

Results and Discussion

When trichloroacetyl chloride is added into a refluxing chloroform solution of 2-picoline N-oxide (2 *M*), a rapid evolution of carbon dioxide (20% yield in 1 hr) occurs. The nmr spectrum of the solution after 1 hr shows the presence of the 2-picolylmethyl trichloroacetate ester (I) (singlet at 5.8 ppm) in about 40% yield. An additional singlet is also present at 5.1 ppm and continued reflux of the original solution leads to continued carbon dioxide formation and a decrease in the 5.8-ppm singlet accompanied by an increase in the 5.1-ppm peak. After a 12-hr reflux, the carbon dioxide yield is 83% and the trichloroacetate ester is nearly completely consumed. The nmr spectrum of the final solution indicated the new product to be present in 70% yield. The isolated yield of this compound is 30–40% after distillation. The product was identified as α-chloro-2-picoline (II) by its spectral properties, boiling point, and picrate.

The ester I, obtained in pure form from 2-pyridylcarbinol and trichloroacetic anhydride, gives II and carbon dioxide on treatment with hydrogen chloride, followed by reflux in chloroform or acetonitrile. When

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(2) P. D. Bartlett and R. R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).

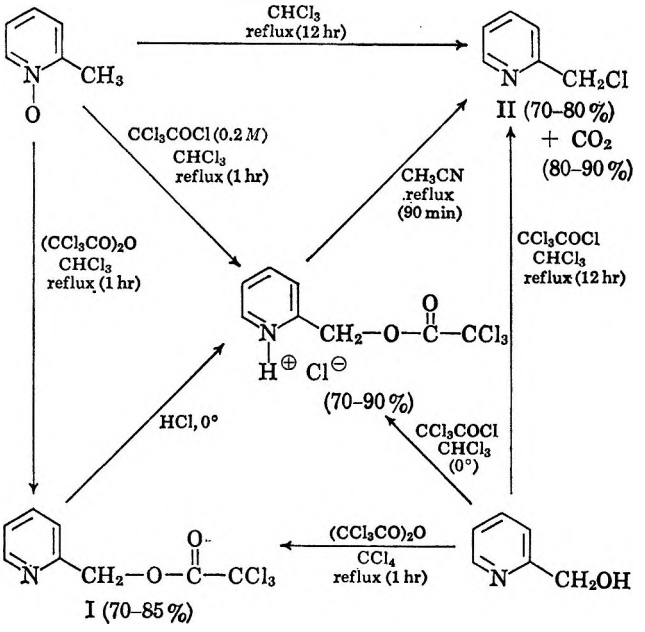
(3) T. Koenig and W. D. Brewer, *Tetrahedron Lett.*, 2773 (1965); T. Koenig and R. Wolf, *J. Amer. Chem. Soc.*, **89**, 2948 (1967).

(4) R. Neuman and J. Behar, *ibid.*, **89**, 4549 (1967).

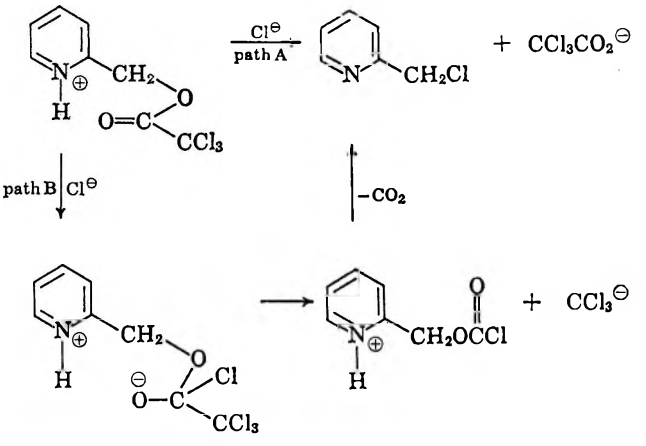
(5) T. Koenig, *ibid.*, **88**, 4045 (1966).

2-pyridylcarbinol is treated with trichloroacetyl chloride, in refluxing chloroform, II is again the product. These results are summarized in Scheme I.

SCHEME I



Two explanations for this rapid substitution process are readily apparent; direct displacement by chloride (path A), or attack of the chloride at the carbonyl followed by loss of the trichloromethyl anion (path B).



Initial control experiments indicated that the rate of decarboxylation of trichloroacetic acid was considerably slower in refluxing chloroform than the carbon dioxide formation in the N-oxide reaction (run 1, Table I).[6] This seemed to rule against path A. However, the trichloroacetate ester of phenol was found to be unreactive in the presence of pyridinum hydrochloride in boiling acetonitrile. This seems to rule against path B.

Reinvestigation of the decarboxylation of trichloroacetic acid with tertiary amines showed that the rates of these reactions depend on both the solvent and concentration (Table I). This is not due to a weak complex formation since the infrared spectrum of a 0.2 *M* solution of the acid and pyridine in chloroform shows no free pyridine to be present; a 10% excess of pyridine can be easily observed (ring band, 1570 cm^{-1}). This concentration dependence is in contrast to the first-order rates usually reported[7] for trichloroacetate salt decomposition.

TABLE I

RATES OF DECARBOXYLATION OF TRICHLOROACETIC ACID

Run	Solvent	Temp, °C	Base[a]	Concn, *M*	*t*/2,[b] min
1	$CHCl_3$	Reflux	Pyridine	0.2	720
2	$CHCl_3$	50	Pyridine	1.0	435
3	$CHCl_3$	51	Pyridine	2.0	173
4	$CHCl_3$	50	Triethylamine	1.0	200
5	CH_3CN	30	Pyridine	2.0	57
6	$(CH_3)_2SO$	30	Pyridine	1.0	18

[a] Amine–acid ratio, 1:1. [b] Time for one-half of the calculate amount of carbon dioxide to be evolved.

At high concentrations, the decarboxylation of trichloroacetic acid in the presence of amines is thus rapid enough to account for the observed behavior of the ester hydrochloride by path A though path B is not rigorously ruled out. When the N-oxide acid chloride reaction is carried out in dilute solution (0.2 *M*), the ester II is obtained in 65% yield even after reflux for 16 hr.

This substitution reaction with trichloroacetyl chloride also occurs with 3-pyridylcarbinol and 4-pyridylcarbinol and benzyl alcohol in the presence of pyridine. However, the 3- and 4-pyridylmethyl chlorides polymerized extensively to give mostly water-soluble tars. Picrates of the corresponding chlorides were obtained from the product mixtures after filtration of the tarry material. 2-Pyridylmethyl acetate does not react with chloride ion under these conditions.

These results indicate that trichloroacetyl chloride can act as a chlorinating agent in a fashion similar to thionyl chloride with added amines. The rapid rate of carbon dioxide formation by this complicated process makes the use of the trichloromethyl side chain a less unambiguous probe for radical *vs.* ionic cleavage of X–O bonds. The present results, however, finally serve to reinforce the previous conclusion that the reaction of picoline N-oxides with acid chlorides and anhydrides does not involve radical-pair intermediates.

Experimental Section

Infrared spectra were obtained using a Beckman IR-5 spectrophotometer. Nuclear magnetic resonance spectra are reported relative to tetramethylsilane, used as an internal standard, with a Varian A-60 spectrometer. All solvents were distilled before use. Trichloroacetic anhydride was obtained from K & K Laboratories and was distilled, bp 49° (0.5 mm). Trichloroacetyl chloride was obtained from the acid by the method of Bosshard.[8] All melting points and boiling points are uncorrected. Analyses were obtained from Berkeley Analytical Laboratories, Berkeley, Calif.

Pyridylmethyl Trichloroacetates.—In a typical run, trichloroacetic anhydride (33.3 g, 0.1 mol) was added to 100 ml of re-

(6) The results of Table I are preliminary. A more complete account of the reaction of trichloroacetic acid with amines in these solvents will be published with data on the reaction of N-oxides with trichloroacetic anhydride in acetonitrile, which gives another variation of the expected behavior. Pyridine N-oxide does not react with trichloroacetic anhydride in refluxing chloroform but reacts rapidly in acetonitrile at 0–30°.

(7) L. Clark, *J. Phys. Chem.*, **63**, 99 (1959); G. Hall and F. Verhoek, *J. Amer. Chem. Soc.*, **69**, 613 (1947); L. Clark, *J. Phys. Chem.*, **64**, 1758 (1960); H. Patwardhan and A. N. Kappanna, *Z. Physik. Chem.* (Leipzig), **A166**, 51 (1933).

(8) H. Bosshard, R. Moroy, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 175 (1959).

TABLE II
ANALYTICAL DATA

Derivative	Mp, °C	Calcd, % C	H	Cl	N	Found, % C	H	Cl	N
Trichloroacetate picrate		34.76	1.88	22.00	11.58				
2-ester	119–120.5					35.02	1.78	21.74	11.36
3-ester	141–143					35.08	1.64	21.76	11.32
Chloride picrate		40.41	2.54	9.94	15.71				
2-chloride	148–150[a]					40.57	2.39	10.03	15.52
3-chloride	129–131[b]					40.55	2.47	9.82	15.44
4-chloride	143–144[c]					40.60	2.37	10.15	15.42
4-Trichloroacetate HCl	126 dec	33.11	2.42	48.60	4.82	33.19	2.29	48.68	4.73

[a] Lit.[9] mp 152–153°. [b] T. Itai and H. Ogura [*J. Pharm. Soc., Japan*, **75**, 296 (1955)] give mp 130.5–132°. [c] H. Mosher and J. Tessieri [*J. Amer. Chem. Soc.*, **73**, 4925 (1951)] give mp 146–147°.

fluxing carbon tetrachloride containing 2-pyridylcarbinol (10.9 g, 0.1 mol). The resulting solution was cooled after 1 hr and neutralized with bicarbonate at 0°, dried, and distilled yielding the ester I as an unstable oil, bp 109–110° (0.5 mm). Its nmr spectrum in deuteriochloroform showed a singlet at 5.5 (two protons) and multiplets centered at 7.5 (three protons) and 8.6 ppm (one proton). Its infrared spectrum in carbon tetrachloride showed carbonyl absorption at 1755 cm^{-1}. A picrate was obtained (Table II), which could be recrystallized from benzene.

The procedure for the 3-pyridylmethyl trichloroacetate was identical. This compound, however, decomposed on attempted distillation. The nmr spectrum of the carbon tetrachloride solution after neutralization showed a singlet at 5.4 (two protons) and multiplets centered at 7.5 (two protons) and 8.4 ppm (two protons). Addition of a weighed amount of dioxane and integration of the nmr peaks indicated the ester was formed in 86% yield. The infrared spectrum of this solution showed carbonyl absorption at 1745 cm^{-1}. A picrate was obtained which was recrystallized from benzene (Table II).

In an identical experiment, a carbon tetrachloride solution of the 4-isomer was obtained (85% yield by nmr). This compound also decomposed on attempted distillation. A hydrochloride was obtained which was purified by sublimation (Table II).

2-Picoline N-Oxide and Trichloroacetyl Chloride.—Trichloroacetyl chloride (11 g, 0.066 mol) was added rapidly to a refluxing solution of chloroform (25 ml) containing freshly distilled 2-picoline N-oxide (5.45 g, 0.05 mol). The reaction was carried out in a closed system with a gas buret attached. Gas evolution was immediately observed and was followed as a function of time. After 21 hr, 1000 ml (80%) of gas had been evolved. The gas was identified as carbon dioxide in separate experiments by absorption on ascarite and by its mass spectrum.

Extraction of the product solution with cold bicarbonate followed by distillation gave a colorless oil [bp 75–77° (12 mm), 30–40% yield] which turned pink after a few minutes and solidified to a red solid after a few hours. The compound was identified as α-chloro-2-picoline (II) by its picrate (Table II) and its nmr spectrum which showed a singlet at 5.1 (two protons) and multiplets centered at 7.5 (three protons) and 8.6 ppm (one proton). The nmr spectrum after the bicarbonate wash indicated the chloride to be present in 70% yield using dioxane as an integration standard.

2-Pyridylmethyl Trichloroacetate Hydrochloride Reaction.—Dry hydrogen chloride gas was passed through a solution of the ester I (2.42 g, 0.01 mol) in acetonitrile at 0°. A white hydroscopic solid precipitated under these conditions and the infrared spectrum of this solid in chloroform showed carbonyl absorption at 1760 cm^{-1} and a broad absorption from 2000–2500 cm^{-1}. This material was refluxed in acetonitrile (0.02 *M*) for 3 hr giving 220 ml of gas and chloride II (75% yield by nmr; picrate, mp 150–151° undepressed).

Pyridylcarbinol-Trichloroacetyl Chloride Reactions.—In a typical run, trichloroacetyl chloride (2.31 g, 0.010 mol) was added to a refluxing solution of acetonitrile (50 ml) and 2-pyridylcarbinol (1.11 g, 0.01 mol) in a closed system with a gas buret attached. Gas evolution was immediately apparent and was 50% complete in 12 min. After 90 min, the evolved gas was 230 ml (92%) and refluxing was discontinued. The nmr spectrum of the resulting solution indicated that the chloride was present in 70% yield. A picrate was obtained (mp 148–150°, undepressed, Table II).

The procedure for the reaction with 3- and 4-pyridylcarbinols was identical. The gas evolution occurred at similar rates and to greater than 90% yield in both cases. The product solutions contained a large amount of solid, but picrates of the corresponding chlorides were obtained after filtration (Table II).

Rates of Trichloroacetic Acid Decarboxylation.—The rates of decarboxylation of trichloroacetic acid were determined in a fashion similar to the above procedures. Stirred solutions of the acid were equilibrated at the temperature of the run in a closed system with a gas buret attached. The amine was added rapidly and the volumes *vs.* time noted.

Registry No.—2-Picoline N-oxide, 931-19-1; trichloroacetyl chloride, 76-02-8; I, 15645-81-5; I (picrate), 15893-35-3; II, 4377-33-7; 3-pyridylmethyl trichloroacetate, 15645-81-5; 3-pyridylmethyl trichloroacetate picrate, 15645-49-5.

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The Reaction of Sulfenyl Chlorides with Allene

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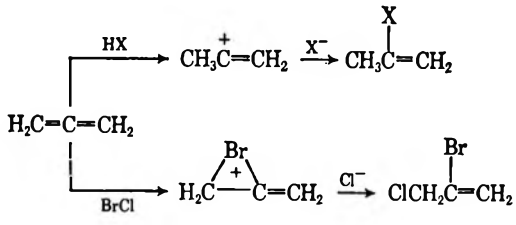
The reaction of either methane-, benzene-, or acetylthiosulfenyl chloride with allene was studied. In all cases allylic chlorides of the general structure I, $CH_2{=}C(SR)CH_2Cl$, were found to be the primary monoadducts. Diadducts of the general structure IV, $RSCH_2(Cl)C(SR)CH_2Cl$, were formed. With the exception of the acetylthiosulfenyl chloride adducts, the monoadducts rearranged to the vinylic chlorides II, $ClHC{=}C(SR)CH_3$; the diadducts IV decomposed rapidly with the loss of HCl. As a consequence of this decomposition, products of the general structure III, $CH_2(Cl)C(SR)CH_2Cl$, were produced. From the reaction of acetylthiosulfenyl chloride and tetramethylallene only the dehydrohalogenated product VI, 2,4-dimethyl-3-acetylthiosulfenyl-1,3-pentadiene, was isolated.

The mechanistic course of electrophilic additions to allene seems to follow one of two paths depending on the nature of the reactant.[3] Addends such as hydrogen halides add with the formation of a vinylic carbonium ion intermediate, resulting in Markovnikov oriented addition products. In contrast, a completely reversed adduct orientation has been observed with interhalogen compounds, *i.e.*, BrCl. Apparently the formation of a bromonium ion and subsequent nucleophilic attack of the chlorode ion on the terminal sp^3 carbon takes place (Scheme I).

SCHEME I



The episulfonium ion intermediate postulated for sulfenyl chloride additions to olefins[4] suggests *a priori* a similar intermediate in additions to allene. Thus, the addition mechanism would be expected to be analogous to that of interhalogens (Scheme I). Indeed, the addition of 2,4-dinitrobenzenesulfenyl chloride to allene has been reported to give 2-(2,4-dinitrobenzenethio)-3-chloro-1-propene.[5] However, similar additions to 1,2-cyclononadiene or 1,2-cyclodecadiene apparently resulted in the opposite adduct orientation, *i.e.*, the vinylic chloride.[6] This discrepancy and the recently recognized strong dependence of sulfenyl chloride–olefin adduct orientation on steric[7] as well as electronic effects[8,9] initiated the present study.

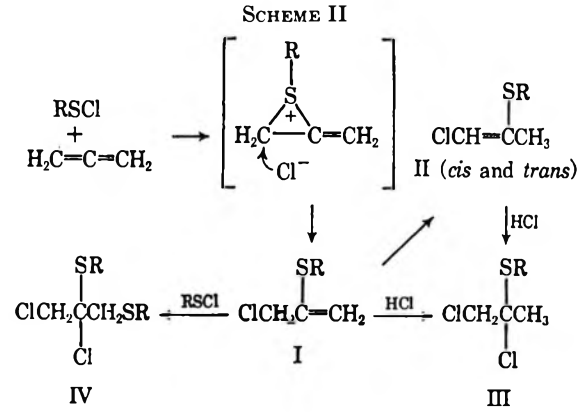
Results and Discussion

Methane-, benzene-, or acetylthiosulfenyl chloride were slowly added to a five- to tenfold excess of allene in methylene chloride. Methane- and benzenesulfenyl chloride reacted spontaneously at −30°, whereas reaction times up to 2 hr were necessary with acetylthiosulfenyl chloride at the same temperature. After it was recognized that the primary products from methane- and benzenesulfenyl chloride were quite labile at ambient temperature, the solvent was removed under vacuum at −10° and the residue analyzed immediately by nmr spectroscopy. This was less critical with acetylthiosulfenyl chloride adducts.

Sulfenyl Chloride–Allene Adducts.—The above described additions afforded four principal products (I–IV). Their relative product distributions obtained are summarized in Table I.

The data show an initial product distribution, *i.e.*, analyzed within 30 min after the addition was completed; values in brackets represent the "final" product distribution. This latter distribution was reached at −20° within 72 hr with the methanesulfenyl chloride adducts and after several weeks with the benzene- and acetylthiosulfenyl chloride adducts. From these data it becomes apparent that there are two primary products, the monoadduct I and the diadduct IV (Scheme II). Both compounds are quite stable if R represents an acetylthio group. In fact, the stability increases depending on R in the following order: $CH_3 < C_6H_5 << CH_3C(O)S$.

SCHEME II



The structure of adduct I is consistent with a product formed by nucleophilic ring opening of the episulfonium ion by the chloride.[7] The possibility of an allylic carbonium ion intermediate cannot be ruled out; however, a significant contribution by a carbonium ion appears unlikely in view of the recently observed 1,2 addition of sulfenyl chlorides to 1,3-dienes[8] and, more importantly, the exclusive *trans* addition to acenaphthylene.[7]

(1) To whom inquiries should be directed.
(2) Analytical Research Division.
(3) K. Griesbaum, *Angew. Chem. Intern. Ed. Engl.*, **5**, 933 (1966), and references therein.
(4) N. Kharasch in "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press Inc., New York, N. Y., 1961, pp 375–396.
(5) T. L. Jacobs and R. N. Johnson, *J. Amer. Chem. Soc.*, **82**, 6397 (1960).
(6) W. R. Moore and R. C. Bertelson, *J. Org. Chem.*, **27**, 4182 (1962).
(7) W. H. Mueller and P. E. Butler, *J. Amer. Chem. Soc.*, **88**, 2866 (1966).
(8) W. H. Mueller and P. E. Butler, *Chem. Commun.*, 646 (1966).
(9) W. H. Mueller and P. E. Butler, *J. Org. Chem.*, **32**, 2925 (1967).

TABLE I
SULFENYL CHLORIDE–ALLENE ADDUCTS

Reactants		% product distribution[a,b]			
RSCl, R	Mole ratio, C_3H_4/RSCl	SR | $ClCH_2C{=}CH_2$ I	SR | $ClHC{=}CCH_3$ II *cis* and *trans*	SR | $ClCH_2C(Cl)CH_3$ III	SR | $ClCH_2C(Cl)CH_2SR$ IV
CH_3–	10	67 [6]	8 [70]	9 [20]	10 [0]
C_6H_5–	5	75 [9]	0 [64]	3 [15]	17 [2]
$CH_3C(O)S$–	10	85 [78]	0 [3]	0 [5]	10 [10]

[a] From semiquantitative nmr analysis within 30 min after reaction; the balance (*ca.* 5%) to 100% remains unidentified. [b] The values in brackets are obtained after postisomerization at −20°.

TABLE II
NMR PARAMETERS OF ALLENE–SULFENYL CHLORIDE PRODUCTS

No.	Structure	R	Chemical shift,[a] ppm H_a	H_b	H_c	R	Coupling constant, cps $J_{a,b}$	$J_{a,c}$	$J_{b,c}$
I	H_aSR | $H_bC{=}CCH_2Cl$ c	CH_3	4.87dt[b]	5.40qt	4.16bd	2.25s	1.60	~0.6	1.92
		C_6H_5	5.25t	5.58t	4.02dd	7.25m	<0.3	0.48	1.20
		$CH_3\overset{O}{\overset{\|}{C}}S$—	5.65dt	5.73m	4.23dd	2.48s	0.63	0.60	1.25
II	$ClH_aC{=}CCH_3$ (*trans*) | SR	CH_3	5.72qt	1.99d		2.24s	1.20		
		C_6H_5	5.93qt	1.89d		7.18m	1.37		
	$H_aC{=}CCH_3$ (*cis*) | Cl SR	CH_3	5.91qt	1.97d		2.27s	1.50		
		C_6H_5	6.24qt	1.62d		7.18m	1.47		
	$SRH_aC{=}CCH_3$[d] | Cl	CH_3	6.04qt	2.10d		2.24s	1.00		
III	$CH_3C(Cl)CH_2Cl$	CH_3	3.92s	1.92s		2.25s			
		C_6H_5	3.77s	1.85s		~7.2m			
		$CH_3\overset{O}{\overset{\|}{C}}S$	3.77s	1.94s		2.48s			
IV	$RSCH_2C(Cl)CH_2Cl$	CH_3	4.12s	3.28s		2.27s			
		C_6H_5	3.93s	3.68s		~7.2m			
		$CH_3\overset{O}{\overset{\|}{C}}S$	4.18s	3.57s		2.48s			
VI	H_aSR | $HC{=}CC{=}C(CH_3)_2$ | CH_3	$CH_3\overset{O}{\overset{\|}{C}}S$	4.57dqt	5.02dqt	2.10bs[c] 1.82*s	2.33s	2.45	0.90	1.45

[a] Abbreviations are s = singlet, d = doublet, t = triplet, qt = quartet, m = multiplet. [b] Since $J_{a,b} = J_{b,c}$, proton H_a appears as a quartet. The small magnitude of $J_{a,c}$ results in partially resolved signals for H_b and H_c. H_a appears as a double triplet and H_c as a broadened doublet. [c] H_c appears as a broad singlet owing to unresolved coupling with H_a and H_b. [d] Registry no.: 15893-18-2.

The formation of diadduct IV from I may not involve an episulfonium ion. In any case, the adduct orientation is electronically controlled and in accord with similar additions of sulfenyl chlorides to vinyl ethers[10] or vinyl sulfides.[11] If R represents methyl or phenyl then diadduct IV is quite labile and decomposes with elimination of HCl. While its characteristic nmr signals disappear those of adduct III increase at a proportional rate. Its formation is due to HCl addition to compounds I and II (Scheme II).

The structural assignments of compounds I, III, and IV are based on nmr evidence primarily. In several cases, particularly in the S-methyl series, structural confirmation was obtained by subsequent independent synthesis.

The nmr spectrum of the methanesulfenyl chloride adduct I is typical of the series (Table II) and gives strong support for the assigned adduct orientation. The terminal methylene group bearing chlorine is a partially resolved double doublet at 4.16 ppm and is coupled allylically to the strongly deshielded terminal olefin protons at 4.87 and 5.40 ppm. The field position of the methylene protons is strong evidence for the terminal chlorine group. A terminal methylene group bearing an S-methyl group would be expected to resonate at *ca.* 0.8 ppm upfield.[12]

Further support for the terminal disubstituted olefinic structure is supplied by characteristic infrared bands at 1605 (C=C stretching[13a]), 3105 (=CH_2

(10) A. Senning and S. O. Lawesson, *Tetrahedron*, **19**, 695 (1963); *Acta Chem. Scand.*, **15**, 1203 (1961); M. J. Baldwin and R. K. Brown, *Can. J. Chem.*, **45**, 1195 (1967).

(11) W. H. Mueller, unpublished data.

(12) P. E. Butler and W. H. Mueller, *Tetrahedron Lett.*, **19**, 2179 (1966).

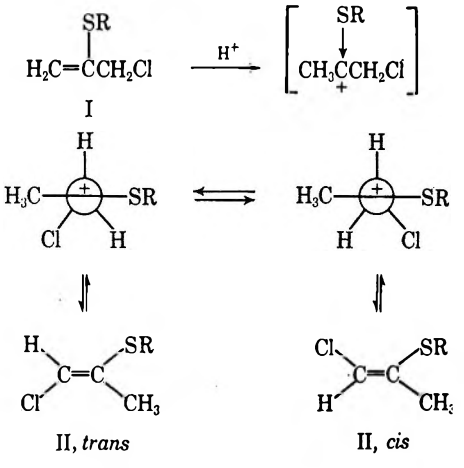
(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1959: (a) p 35; (b) p 51; (c) p 36.

stretching[13b]), and 862 cm^{-1} (=CH_2 out-of-plane hydrogen deformation[13b]).

The nmr spectra of the S-methyl compounds III and IV consist of three singlets (Table II) with intensities and field positions identical with those of independently synthesized samples. Product IV was obtained from the reaction of 2 equiv of either methane- or acetylthiosulfenyl chloride with allene. The diadduct formed from the latter sulfenyl chloride proved quite stable at ambient temperature, whereas the methanesulfenyl chloride diadduct decomposed rapidly even at −20° with the evolution of gaseous HCl and black tar. Hydrogen chloride addition to the S-methyl analog of II, whose independent synthesis is described below, produced a product identical with III.

Rearrangement of Monoadduct I.—As indicated above, there is a correlation between the stability of adducts I and IV with the electronic character of R. A similar relationship had been found previously for the propensity for rearrangement of sulfenyl chloride adducts from olefins[7,9] and conjugated dienes.[8] This has been attributed to the relative electron availability on the sulfur atom toward SNi displacement of the respective β-chlorides. The same factors may be envoked to provide a rationale for the stability or ease of formation of the intermediate carbonium ion (Scheme III) postulated for the rearrangement of adduct I to compound II.

SCHEME III



The kinetically controlled product of this acid-catalyzed rearrangement is the *cis* isomer of II. At a low conversion level (*ca.* 20% rearranged), compound *cis* II was the exclusive product if R was phenyl. When R = methyl, a 4:1 *cis/trans* ratio was observed at the same conversion. When adduct I, however, had rearranged to the extent of >90% a 1:1 and 3:2 *trans/cis* isomer ratio was observed with R being phenyl and methyl, respectively. This represents the equilibrium mixture of the two isomers since the same ratio was obtained independently from the acid-catalyzed isomerization of the pure *trans*-S-methyl compound, II. This compound was available from the addition of methanesulfenyl chloride to methylacetylene.

Infrared analysis indicated the trisubstituted olefin for II. Characteristic peaks are at 1605 (C=C stretching) and 795 cm^{-1} (=CH— out-of-plane hydrogen deformation).[13c]

The nmr data confirmed this structural assignment. The allylic methyl hydrogens of the *trans* isomer II exhibit a doublet at 1.99 ppm coupled *trans* to the vinylic proton (J = 1.20 cps) which appears as a quartet at 5.72 ppm. The *cis* isomer shows a doublet for its methyl hydrogens at 1.97 ppm which is coupled to the *cis* oriented vinylic hydrogen (J = 1.50 cps). Its signal appears as a quartet at 5.91 ppm.

The anti-Markovnikov adduct orientation and *trans* stereochemistry are assigned by analogy to similar additions with dimethylphosphorylsulfenyl chloride[14] or dimethylaminosulfenyl chloride.[15] The dependence of product orientation on solvent has recently been reported.[16] In general, *trans* addition of sulfenyl chlorides to acetylenes has been assumed.[16,17]

Acetylthiosulfenyl Chloride–Tetramethylallene Adduct.—To our knowledge the reaction of 2,4-dinitrobenzenesulfenyl chloride with cyclic allenes[6] is the only previously reported example of such additions to substituted allenes. It is quite surprising that this addition should result in Markovnikov oriented monoadducts, *i.e.*, the opposite adduct orientation as now observed in several cases with allene. Ring opening of an episulfonium ion intermediate on the vinylic carbon or a vinyl carbonium ion as postulated for hydrogen halide additions (Scheme I) does not offer an attractive explanation, particularly since little evidence for the occurrence of carbonium ion intermediates was found throughout our previous work on sulfenyl chloride additions to olefins[7] and dienes.[8]

Tetramethylallene was thought to provide a convenient model reagent to study the effect of terminal substituents on the adduct orientation. Acetylthiosulfenyl chloride was chosen as the addend since it had afforded the most stable adducts with allene. Although the addition reaction appeared to proceed in a normal fashion, the subsequent product elucidation became unexpectedly complicated. The reaction mixture rapidly evolved HCl at ambient temperature. Compound VI (Scheme IV) was the sole identifiable product and was isolated in *ca.* 80% yield.

The structure of the diene VI was revealed by its nmr spectrum (Table II). A singlet at 2.10 ppm appears for the vinylic methyl group, and a more shielded singlet at 1.82 ppm of twice the intensity represents the two terminal methyl groups. Two double quartets at 4.57 and 5.02 ppm are characteristic for the nonequivalent terminal methylene protons.

The nmr spectrum of the crude product mixture at low temperature is quite complex containing a number of methyl group signals. Signals pertinent for compound VI indicate its presence in this crude product and some of the additional methyl group singlets are consistent with structure V; however, a definite assignment was not possible. In view of the questionable intermediacy of the expected primary adduct V, an additional pathway for the formation of product VI has to be considered (Scheme IV). Expulsion of a proton from either an episulfonium ion or carbonium ion inter-

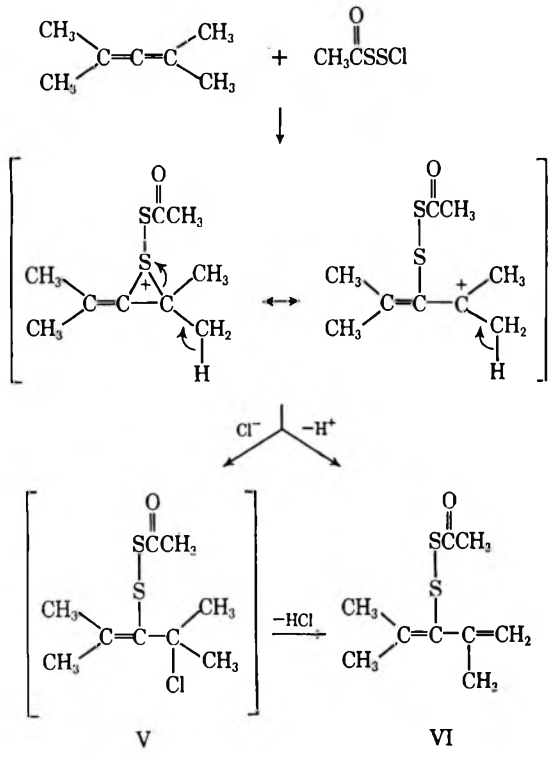
(14) W. H. Mueller, R. M. Rubin, and P. E. Butler, *J. Org. Chem.*, **31**, 3537 (1966).

(15) W. H. Mueller and P. E. Butler, β-Chloroalkylsulfenamides, *ibid.*, in press.

(16) V. Calò, G. Melloni, G. Modena, and G. Scorrano, *Tetrahedron Lett.*, **49**, 4399 (1965), and references therein.

(17) N. Kharasch and C. N. Yianios, *J. Org. Chem.*, **29**, 1190 (1964).

SCHEME IV



mediate provides an alternate mechanism for the formation of VI. A significant contribution of an allylic carbonium ion structure to the intermediate in this special case is conceivable, particularly in view of previous work with acetylthiosulfenyl chloride.[9] It had been found that the withdrawing effect of the acetyl group tends to destabilize a positive charge on the sulfur atom in an episulfonium ion, thus contributing to the development of an electron deficient center on an alkyl-substituted carbon atom. This resulted in predominant Markovnikov addition to isobutylene.

Although the present result in the case of tetramethylallene does not rigorously exclude the possibility of Markovnikov addition (*i.e.*, vinylic chloride) to alkyl-substituted allenes, it is consistent with the normal adduct orientation observed with the parent allene.

Experimental Section

Method of Analysis.—Nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer. Neat samples containing tetramethylsilane as an internal standard were used unless stated otherwise.

Infrared spectra were recorded on a Beckman Model IR-10 infrared spectrophotometer.

Starting Materials. Unsaturates.—The allene used was a Matheson product of +99% purity. It contained *ca.* 0.8% propene and traces of propane. Tetramethylallene (*ca.* 98% pure) was obtained from Columbia Organic Chemicals Co.

Methanesulfenyl Chloride.—Its previously reported preparation[18] from dimethyl disulfide and sulfuryl chloride was slightly modified by omitting tetrachloroethane as a solvent. The distilled methanesulfenyl chloride was obtained in *ca.* 90% yield and +98% purity. Its nmr spectrum shows a singlet at 2.91 ppm.

Benzenesulfenyl Chloride.—Freshly distilled sulfuryl chloride (20.3 g, 0.15 mol) was slowly added at ambient temperature to a solution of 32.7 g (0.15 mol) of diphenyl disulfide in 100 ml of CH_2Cl_2 (dry) containing 3 ml of pyridine.[19] After completion of the addition, the solution was stirred for an additional hour and then the solvent was removed at ambient temperature (12 mm). Subsequent distillation of the residue afforded 33 g (76% yield) of the dark red benzenesulfenyl chloride: bp 49° (4 mm); $n^{20}D$ 1.613 [lit.[20] $n^{20}D$ 1.610).

Acetylthiosulfenyl Chloride.—The chlorination of diacetyl disulfide afforded acetylthiosulfenyl chloride of *ca.* 99% purity.[9] The only impurity present was the starting disulfide.

General Method of Addition of Sulfenyl Chlorides to Unsaturates.—To an approximately 50% solution of the unsaturate in methylene chloride, the sulfenyl chloride was slowly added at such a rate to keep the reaction mixture at −30 to −40°. Anhydrous conditions and a nitrogen atmosphere were maintained. Approximately a 9 *M* excess of the unsaturate was used for the selective synthesis of monoadducts. Diadducts were obtained from stoichiometric amounts of reactants. Addition of methane- and benzenesulfenyl chloride to the unsaturates was strongly exothermic and instantaneous. After removal of most of the solvent at *ca.* −10° (2 mm) the crude product mixtures were analyzed immediately by nmr spectroscopy. Similar additions using acetylthiosulfenyl chloride were found to be much slower. In case the reaction mixtures were kept for 2 hr at −30° after the addition was completed. The reaction mixtures were then allowed to warm to room temperature, and the solvent was removed on a rotary evaporator.

The crude product mixtures were analyzed by nmr. Essentially quantitative consumption of the sulfenyl chlorides was observed. Product distributions and nmr parameters of the individual adducts are summarized in Tables I and II, respectively.

1-Chloro-2-methylthio-1-propene (*trans* II).—Addition of methanesulfenyl chloride to methylacetylene according to the above procedure afforded the *trans* adduct II in >95% selectivity together with <5% of the isomeric 1-methylthio-2-chloro-1-propene. Distillation under vacuum yielded the *trans* adduct II, bp 58° (32 mm).

Anal. Calcd for C_4H_7SCl: C, 39.18; H, 5.71; S, 26.15. Found: C, 39.09; H, 5.98; S, 26.04.

1,2-Dichloro-2-methylthiopropane (III).—Gaseous HCl was bubbled through 1-chloro-2-methylthio-1-propane (II) and the conversion was followed by nmr analysis. After the reaction was completed, the product was briefly degassed at reduced pressure. The tan, liquid compound slowly darkened (24 hr at room temperature); however, no sign of decomposition was observed in its nmr spectrum.

Anal. Calcd for $C_4H_8SCl_2$: C, 30.20; H, 5.09; S, 20.16. Found: C, 30.31; H, 5.18; S, 19.95.

***trans–cis* Isomerization of 1-Chloro-2-methylthio-1-propene** (II).—Gaseous HCl was introduced into pure *trans* adduct II until 5–10% of II was converted into the HCl adduct III. The isomerization of *trans* into *cis* adduct II was then followed by nmr analysis. Within 8 hr at room temperature, equilibrium was reached at a *cis*/*trans* ratio of 2:3.

2-Acetylthiosulfenyl-3-chloro-1-propene (I).—Acetylthiosulfenyl chloride was added to allene as described in the general procedure. Distillation of the crude product under vacuum afforded pure monoadduct I, bp 64–65° (0.02 mm).

Anal. Calcd for $C_5H_7S_2OCl$: C, 32.87; H, 3.86; S, 35.10. Found: C, 32.59; H, 3.79; S, 35.63.

1,2-Diacetylthiosulfenyl-2,3-dichloropropane (IV).—Addition of 2 equiv of acetylthiosulfenyl chloride to allene according to the general procedure resulted in the diadduct IV. It was not possible to distil the oily product, however, small amounts of volatile impurities were removed with nitrogen bubbling at room temperature (*ca.* 10^{-4} mm).

Anal. Calcd for $C_7H_{10}S_4O_2Cl_2$: C, 25.84; H, 3.01; S, 39.42. Found: C, 25.67; H, 3.01; S, 40.01.

2,4-Dimethyl-3-acetylthiosulfenyl-1,3-pentadiene (VI).—The addition of acetylthiosulfenyl chloride to tetramethylallene was carried out as described in the general procedure. The crude product evolved HCl at room temperature which was facilitated by decreased pressure and moderate heating (*ca.* 60°). Once a constant vacuum could be maintained distillation became possible. The dehydrohalogenated product VI was attained in *ca.* 80% yield at bp 63–64° (5×10^{-3} mm).

(18) H. Brintzinger, K. Pfannstiel, H. Koddebusch, and K. Kling, *Ber.*, **83**, 87 (1950).

(19) N. Kharasch, U. S. Patent 2,929,820 (1960); *Chem. Abstr.*, **54**, 15318 (1960).

(20) I. B. Douglass, K. R. Brower, and P. I. Murrin, *J. Amer. Chem. Soc.*, **74**, 5770 (1952).

Anal. Calcd for $C_9H_{14}S_2O$: C, 53.42; H, 6.97; S, 31.69. Found: C, 52.96; H, 6.90; S, 31.90.

Registry No.—Allene, 463-49-0; methanesulfenyl chloride, 5813-48-9; benzenesulfenyl chloride, 931-59-9; acetylthiosulfenyl chloride, 3250-24-3; I (R = CH_3), 15893-05-7; I (R = C_6H_5), 15893-06-8; I (R = CH_3COS), 15893-07-9; II (R = CH_3) (*trans*), 15893-08-0; II (R = C_6H_5) (*trans*), 15893-09-1; II (R = CH_3) (*cis*), 15893-10-4; II (R = C_6H_5) (*cis*), 15893-11-5; III (R = CH_3), 15893-12-6; III (R = C_6H_5), 15893-13-7; III (R = CH_3COS), 15893-14-8; IV (R = CH_3), 15893-15-9; IV (R = C_6H_5), 15893-16-0; IV (R = CH_3COS), 15893-17-1; VI, 15822-80-7.

Acknowledgment.—The authors thank Mr. W. C. Whitlock for excellent technical assistance.

The Structure of Di(benzenesulfonyl)hydrazines and the Synthesis and Characterization of Di(phenylsulfonyl)diimide, a New Azo Compound[1-3]

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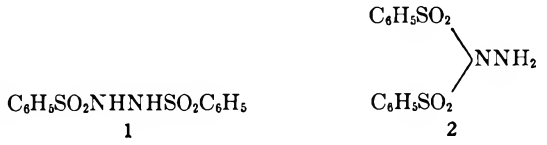
Evidence provided by nmr, mass spectrometry, ultraviolet, infrared, and pK_a measurements on dibenzenesulfonylhydrazine has been evaluated in the effort to distinguish between the symmetrical and unsymmetrical formulations possible for this substance. A clear-cut distinction on the basis of these physical lines of evidence alone has not been found possible. However, on mild oxidation it is shown that di(phenylsulfonyl), **11**, is produced in good yield. The formation of this oxidation product, which could not have arisen from the unsymmetrical structure **2** except by an unprecedented rearrangement of a benzenesulfonyl group, is regarded as proof of the originally proposed structure **1**. The structure proof for **11**, based on elemental analysis, molecular weight determination, nmr, ir, Raman, and mass spectral evidence, appears to contradict earlier statements in the literature that such azo compounds are synthetically unstable.

Several groups of workers[4-6] have reported a preparation alleged by Curtius[4] to be **1**, the summetrically substituted N,N′-bisbenzenesulfonylhydrazine, by reacting benzenesulfonyl chloride with hydrazine in alkaline solution.[5,6] However, the only evidence presented in support of their proposed structure was an elemental analysis and a molecular weight determination. The possibility that the unsymmetrical isomer **2** had been formed was not considered by these early workers.



$C_6H_5SO_2NHNHSO_2C_6H_5$ (**1**) $\qquad$ $C_6H_5SO_2\backslash NNH_2 / C_6H_5SO_2$ (**2**)

Recent results reported by Smith and Hein[6] for analogous sulfone–hydroxamic acid reactions suggest the need to consider the alternative structure **2**. A clear distinction in the behavior of corresponding sulfonyl and carbonyl derivatives undergoing acylation reactions has been demonstrated. Thus, Smith and Hein[7] showed that, whereas acylation of sulfonehydroxamic acids proceeded by oxygen substitution, further substitution occurred at nitrogen faster than O-acylation of the unsubstituted hydroxamic acid. Finally, in these laboratories,[8] it has been established that the reaction of sulfonehydroxamic acids with toluenesulfonyl chlorides results exclusively in the N,N-bis(toluenesulfonyl)hydroxylamine.

The only basis for a choice between structures **1** and **2** has been proposed by Grammaticakis[9] in studies of the absorption of α,β-disubstituted hydrazines in the visible and ultraviolet. He has claimed, in effect, that uv spectral similarities between benzenesulfonamide and the Curtius product, dibenzenesulfonylhydrazine, can be construed to support structure **1**.

Results and Discussion

Ultraviolet Spectra.—In reexamining the basis of Grammaticakis' deduction, the spectral characteristics of dibenzenesulfonylhydrazine were compared with those of benzenesulfonamide (**3**) and dibenzenesulfonimide (**4**) (see Figure 1). It will be noted that all three spectra possess a shoulder on the short wave length side of λ_{max}. Furthermore, the λ_{max} positions and intensities are almost identical in all three cases. Clearly the strong similarity in the spectral features of the imide **4** and the amide **3** tends to vitiate the Grammaticakis argument in support of structure **1**. His interpretation, which makes the implicit assumption that the presence on the nitrogen atom of only a single acyl or sulfonyl group is responsible for the observed relationship in the uv characteristics of the Curtius product and benzenesulfonamide (**3**), is obviously unfounded. Thus, formula **2** is still admissible on the basis of the uv evidence as a possible structure of dibenzenesulfonylhydrazine.

Mass Spectroscopy.—For this purpose the homologous di-*p*-toluenesulfonylhydrazine (**1a**) was employed. The objective again was to determine whether

(1) This name is chosen to be consistent with the nomenclature usage set forth in *Chemical Abstracts*. However, the common name azobisdiarenesulfones appears to be somewhat established in the literature.[2]

(2) H. Bock, *Angew. Chem.*, **77**, 472 (1965), see ref 3. This reference was kindly supplied by a very knowledgeable referee.

(3) These reaction conditions were very similar to those employed commonly in the Diels–Alder condensation reactions of cyclopentadiene with azobisdiformate esters. See for examples (a) J. G. Kuderna, U. S. Patent 2,802,012 (1957); (b) J. G. Kuderna, J. W. Sims, J. F. Wikstrom, and S. B. Soloway, *J. Amer. Chem. Soc.*, **81**, 382 (1959); (c) O. Diels, J. H. Blum, and W. Koll, *Ann.*, **443**, 242 (1925); (d) J. C. J. Mackenzie, A. Rodgman, and G. F. Wright, *J. Org. Chem.*, **17**, 1666 (1952); (e) A. Rodgman and G. F. Wright, *ibid.*, **18**, 465 (1953).

(4) T. Curtius and F. Lorenzen, *J. Prakt. Chem.*, **58**, 166 (1898).

(5) K. F. Jennings, *J. Chem. Soc.*, 1172 (1957).

(6) O. Hinsberg, *Ber.*, **27**, 601 (1894).

(7) P. A. S. Smith and G. E. Hein, *J. Amer. Chem. Soc.*, **82**, 5731 (1960).

(8) B. E. J. Schultz, M. S. Thesis, University of Delaware, 1963.

(9) P. Grammaticakis, *Bull. Soc. Chim. Fr.*, 93 (1953).

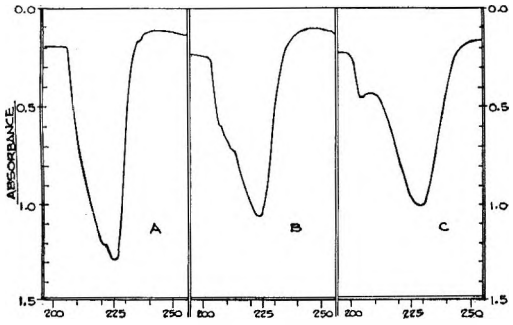
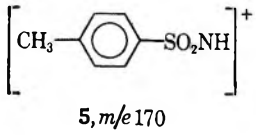


Figure 1.

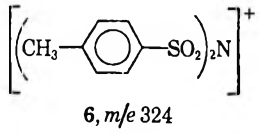
a clear distinction was possible between the symmetrical and unsymmetrical formulations of the structure of this product. Figure 2 presents that portion of the mass spectrum obtained for the interval from *m/e* 50 to the parent peak at 340. Expectedly, the masses below 200 are far more abundant (the scale *m/e* 190–340 has been magnified ten times).

This spectrum must be examined in terms of what masses could be anticipated to appear in greater relative abundance for each of the structural alternatives. Thus, for the (homologous) structure **1**, the fragment **5**, arising from symmetrical cleavage at the N–N bond, could have been anticipated (or some related fragment possessing several hydrogens more or



5, *m/e* 170

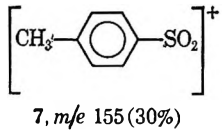
less). For the unsymmetrical homolog of **2**, the fragment **6** representing the cleavage of the N–N bond could be anticipated (or some related fragment possessing one or more additional hydrogens).



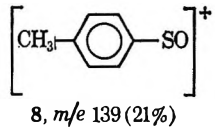
6, *m/e* 324

However, the actual findings are not in clear-cut, exclusive agreement with either expectation, and cannot therefore be regarded as a decisive basis for distinction between the alternative structures **1** and **2**. Thus, peaks are found at *m/e* 172 (relative abundance 15%) and *m/e* 326 (0.1%). The *m/e* 326 peak could be construed to be in support of both alternatives since it could also have arisen as a rearrangement product of structure **1**.

Other peaks that are to be noted in the spectrum can be reconciled as fragmentation products of either structure. For instance, the relatively intense peaks at *m/e* 155 and 139 are to be correlated with the fragments **7** and **8**, sulfone and sulfoxide moieties. Peaks

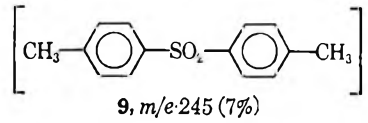


7, *m/e* 155 (30%)

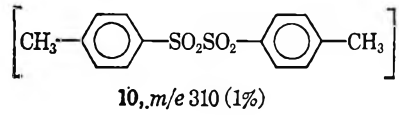


8, *m/e* 139 (21%)

at *m/e* 245 and 310 can be identified with the fragments **9** and **10** which could conceivably have originated from either precursor (**1** or **2**).



9, *m/e* 245 (7%)



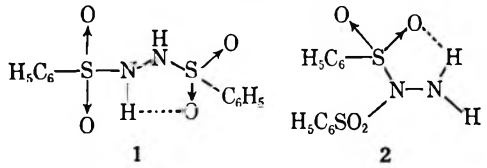
10, *m/e* 310 (1%)

Nmr Spectroscopy.—In acetone solution in the A-60 the hydrazine derivative from benzenesulfonyl chloride displayed a multiplet of relative area 5 centered near 7.75 ppm (phenyl protons) and a poorly resolved peak near 8.82 ppm of relative area 1 (N–H protons). The corresponding *p*-tolyl derivative, examined in the 100-Mc instrument, showed the aromatic protons as a clearly defined AB quartet and the N–H protons appeared downfield as a relatively sharp singlet.

These observations would suggest that the true structure of the Curtius compound possesses a highly acidic N–H proton. This is confirmed by measurement of the pK_a (6.45), but, again, it is not possible to deduce with any confidence whether this fact is in better agreement with either of the alternatives being considered.

Hydrogen Bonding.—In dilute carbon tetrachloride solution it was possible to identify both an intramolecularly bonded N–H at 3300 and a free N–H at 3390 cm^{-1}. In dilute tetrahydrofuran the intramolecular bond disappeared (as usual) and an intermolecular bond (to the THF) at 3350 cm^{-1} replaced it. A $\Delta\nu$ value of 90 cm^{-1}, however, can be reconciled with either of the hydrogen bonded versions of **1** or **2**, as seen in Scheme I.

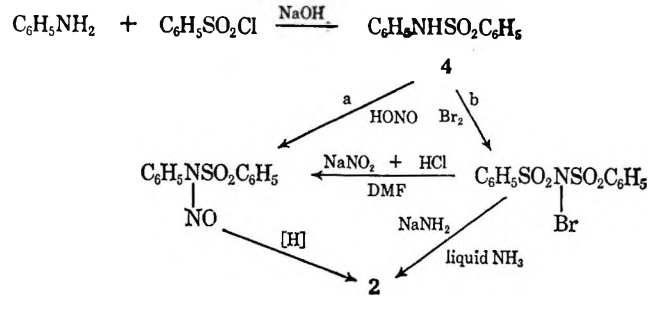
SCHEME I
INTRAMOLECULAR H BONDING



1 **2**

Structure Proof *via* Synthesis.—Two approaches were undertaken in the effort to establish the structure of the Curtius product through the use of common preparative procedures and structural transformations. The first attempt was directed toward an independent synthesis of structure **2** through the route outlined in Scheme II.

SCHEME II



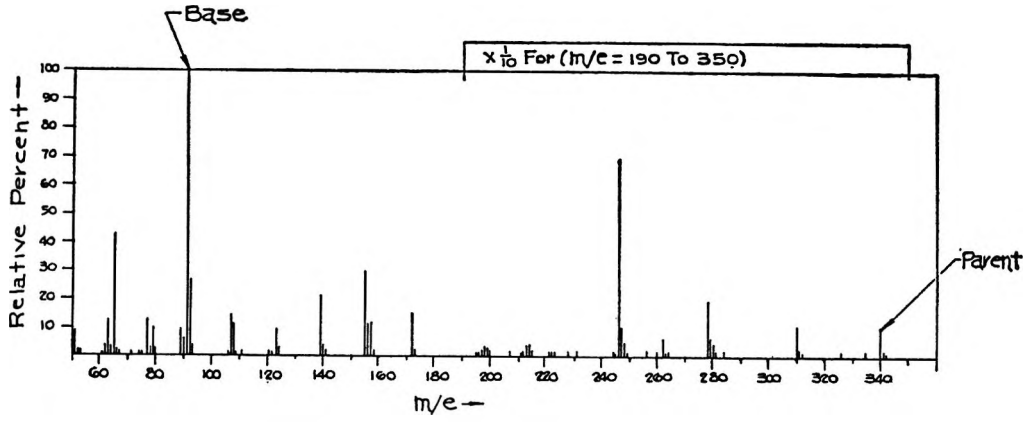


Figure 2.—Mass spectrum of dibenzenesulfonylhydrazine.

TABLE I

Reacn no.	Nitrosating agent	Compd reacted	Solvent	Temperature, °C	Product	Ref
1	HNO_2 + HCl	$(C_6H_5SO_2)_2NH$	Water	0	$(C_6H_5SO_2)_2NH$	*a*
2	HNO_2 + dry HCl	$(C_6H_5SO_2)_2NH$	C_2H_5OH	0	$(C_6H_5SO_2)_2NH$	*a*
3	HNO_2 + dry HCl	$(C_6H_5SO_2)_2NH$	DMSO[b]	0	$(C_6H_5SO_2)_2NH$	*c*
4	HNO_2 + dry HCl	$(C_6H_5SO_2)_2NH$	DMF[d]	0	$(C_6H_5SO_2)_2NH$	*c*
5	HNO_2 + dry HCl	$(C_6H_5SO_2)_2NBr$	DMSO	0	$(C_6H_5SO_2)_2NH$	*c*
6	HNO_2 + dry HCl	$(C_6H_5SO_2)_2NBr$	DMF	0	$(C_6H_5SO_2)_2NH$	*c*
7	Isoamyl nitrite + dry HCl	$(C_6H_5SO_2)_2NBr$	Ether	40	$(C_6H_5SO_2)_2NH$	*e*
8	Isoamyl nitrite + dry HCl	$(C_6H_5SO_2)_2NH$	Ether	0–40	$(C_6H_5SO_2)_2NH$	*e*
9	Nitrosyl sulfuric acid	$(C_6H_5SO_2)_2NH$	Water	0	$(C_6H_5SO_2)_2NH$	*a*, *e*

[a] W. W. Hartman and L. J. Roll, "Organic Syntheses," Coll Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 460. [b] DMSO was dried over a molecular sieve and distilled under vacuum. [c] N. Kornblum, *et al.*, *J. Amer. Chem. Soc.*, **78**, 1497 (1956); N. Kornblum and J. W. Powers, *J. Org. Chem.*, **22**, 455 (1957). [d] DMF was dried over calcium hydride and distilled. [e] N. Levin and W. H. Hartung, "Organic Syntheses," Coll Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 191; W. H. Hartung and J. C. Munch, *J. Amer. Chem. Soc.*, **51**, 2262 (1929); W. H. Hartung and F. Crossley, "Organic Syntheses," Coll Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 363.

Dibenzenesulfonimide (**4**) was prepared by a method analogous to that of Dykhanov.[10] The structure of **4** was in complete agreement with its nmr spectrum showing a phenyl proton multiplet of relative area 10 at 7.42–8.25 ppm and an N–H peak of relative area 1 at 11.1 ppm. However, all attempts to convert it into the N-nitroso derivative through route a or b failed. The various attempts, both successful and unsuccessful, made to carry out each of the steps in Scheme II summarized in Table I (see Experimental Section).

The second effort was directed at transforming the Curtius compound to a product which could be unequivocally identified, and its structure related to that of the starting material by means of the nature of the transforming reaction. It has been pointed out[2] that other investigators have attempted to oxidize the hydrazine derivative **1** in the effort to obtain the corresponding azo compound and have reported decomposition of the presumed reaction product even at −50°. In our hands, however, this objective could be accomplished in ideal fashion through the use of bromine at refluxing ethanol temperatures.

The proof of the structure of **11** then clearly establishes the structure **1** for its hydrazine precursor, unless the obtuse assumption be made that structure **2** could be transformed to **11** *via* oxidative rearrangement of a benzenesulfonyl group in the unsummetrical hydrazine. The migration of groups, which normally show high migration tendency in passing from one nitrogen to the other in unsymmetrically disubstituted hydrazines, has recently been reviewed by Lemal.[11] However, the substrates and reaction conditions under which such rearrangements can be effected are quite different than those which bring about formation of **11**. Moreover, the rearrangement of a benzenesulfonyl group in a 1,2 shift of this nature will be recognized as quite unprecedented.[11]

$$1 \xrightarrow[\text{ETOH}]{Br_2} C_6H_5SO_2N{=}NSO_2C_6H_5 + 2HBr$$

11

Proof of Structure and Characterization of Di(phenylsulfonyl)diimide. A. Analysis.—The elemental analysis involving direct determination of the elements (C, H, O) and ebullioscopic determination of molecular weight (mol wt, 299 *vs.* 310 calcd) are completely consistent with a dehydrogenation product of **1**, rather than some dimeric oxidation product. The possibility that the oxidation of **1** may have proceeded to the *azoxy* stage is ruled out by the direct determination of the oxygen content of **11** (see Experimental Section).

B. Nmr Data.—The spectrum consisted of only phenyl protons in the usual multiplet relationship at *ca.* 7.7–8.0 ppm. This is again in accord with the assigned structure **11**.

C. Ir Data.—The spectrum was devoid of an –N–H absorption and had instead a prominent and very

(10) N. N. Dykhanov, *Zh. Obshch. Khim.*, **29**, 3602 (1959); *Chem. Abstr.*, **54**, 19577*h* (1960).

(11) D. M. Lemal, F. Menger, and E. Coats, *J. Amer. Chem. Soc.*, **86**, 2395 (1964).

TABLE II
ELEMENTS OF COMPARISON AND CONTRAST IN THE MASS SPECTRA[a] OF THE SUBSTRATE HYDRAZINE AND ITS OXIDATION PRODUCT

Dibenzenesulfonylhydrazine (1)			Di(phenylsulfonyl)diimide (11)		
Relative[b] approximate intensity	*m/e*	Possible identity	Possible identity	*m/e*	Relative[b] approximate intensity
0.3	313	Ion molecule reaction of P		Missing	...
0.4	312	P		Missing	...
0.2	282	P − $(NH)_2$	P − N_2	282	48
4	250	P − (2N + 2O + 2H)	P − (2N + 2O)	250	7
...	Missing		P − (SO + 2N)	234	99
0.7	218	P − (SO_2NHNH)		Missing	...
3	171	Cleavage ($C_6H_5SO_2NHNH^+$; $C_6H_5SO_2NN$ + 2H) or rearrangement product	Ion–molecule reaction?	171	29
100	142	$C_6H_5SO_2H^+$	Ion–molecule reaction	142	15
14	141	$C_6H_5SO_2^+$		141	100
43	125	$C_6H_5SO^+$		125	36

[a] Spectra were obtained with a direct injection probe on the CEC 21-103C mass spectrometer. For compound 1 the results recorded are from runs with probe temperatures of 180–210°. For compound 11 which was thermally (relatively) unstable the probe temperature was approximately 100°. The usual isotope peaks are not listed in this comparison table. [b] The peaks of compounds 1 and 11 are not to be compared to each other in any absolute sense since their recorded spectra were not run under precisely the same conditions. For instance, under exactly the same conditions the 142 peak of 11 is only *ca.* 1/20 as intense as that from 1.

sharp band at 1575 cm^{-1} known[12] to be characteristic of the disubstituted azo grouping.

The presence of this band, which we and others[12] have shown to be absent in the ir spectrum of azobisdiformamide, azobisisobutyronitrile, and diisopropyl azobisdiformate, would suggest that at least part of the composition of **11** has the *cis* structure about the —N=N— bond; otherwise, as in the cases of the other symmetrically substituted *azo* compounds, the —N=N— (unconjugated) stretch would be infrared inactive. (See Raman spectra below). The occurrence of an attractive sulfone-sulfone interaction stabilizing the *cis* configuration (**11a**) is apparently quite unique. The analogous carbonyl and cyano bearing substituents on the azo group are mutually repulsive and exist exclusively in the *trans* configuration.[12c]

It must also be noted that the ir spectrum of **11** does not of itself exclude an azoxy structure, but the intense 1575-cm^{-1} band makes this structure much less probable in consideration of the great variety of unsymmetrical azo compounds correlated with this absorption by LeFevre and coworkers.[12]

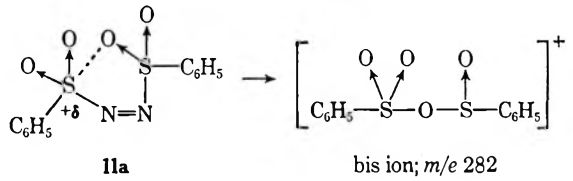
D. Raman Spectrum.—The azo (unconjugated) stretch in **11** is also strongly active in the Raman spectrum at 1576 cm^{-1}. This observation affords direct support for the presence of *trans* configuration material in the composition of the oxidation product. Furthermore, azobisdiformamide and diisopropyl azobisdiformate also show very strong absorptions at 1575 cm^{-1} in the Raman spectrum, which establish for both of these structures the symmetrical *trans* configuration about the double bond arrived at tentatively by LeFevre and coworkers[13c] on the basis of other measurements.

Judging roughly from the ratio of intensities of the $-SO_2-$ band at 1150 cm^{-1} and the 1576-cm^{-1} absorption, the oxidation product was comprised of two-thirds *trans* and one-third *cis*. This is further born out by direct petrographic microscope examination of the oxidation product, showing two types of crystals in the approximate ratio confirmed by these Raman band intensities.

E. Mass Spectrum.—In seeking verification of the structure of **11** a comparison of its spectrum with that of the precursor hydrazine proved to be most informative (see Table II).

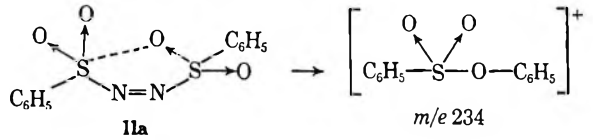
The relatively weak intensity peak at *m/e* 282 in **1** is explained as the product of extrusion of –NH–NH–, as commented on earlier in connection with the spectrum of di-*p*-toylsulfonylhydrazine (see above). This is one of the strongest peaks in the spectrum of **11** in the same mass range. The ready expulsion of nitrogen from the parent ion of azobisarylsulfone to give the bis ion (see Scheme III) accounts for the total absence of P in the spectrum of **11** and represents just what one would have expected of a molecule of its structure. That is to say, in view of the ir and Raman spectral evidence demonstrating the interaction that stabilizes the *cis* structure **11a**, the large extent of formation of the bis ion is made understandable.

SCHEME III



11a bis ion; *m/e* 282

The second most abundant peak of **11** in this mass range is actually missing in the spectrum of **1**, namely, *m/e* 234. This must represent the alternative manner of recombination of radical ion fragments produced in the nitrogen extrusion from **11a** accompanied by expulsion of SO.

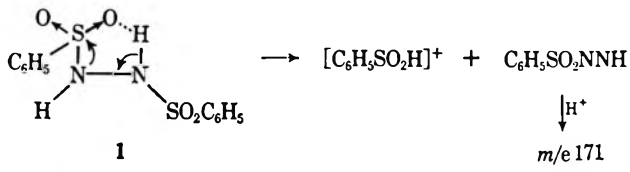


11a *m/e* 234

The most abundant peak of **1** may be correlated with the occurrence of intramolecular hydrogen bonding (identified above for **1**) which cannot occur in **11**.

(12) (a) R. J. W. LeFevre, M. F. O'Dwyer, and R. L. Werner, *Chem. Ind.* (London), 378 (1953); (b) R. J. W. LeFevre, M. F. O'Dwyer, and R. L. Werner, *Aust. J. Chem.*, **6**, 341 (1953); (c) R. J. W. LeFevre, C. G. LeFevre, and W. T. Oh, *ibid.*, **10**, 218 (1957).

Thus, with the formation of *m/e* 142, a cleavage product can also be regarded as a rearrangement result. Azo compound **11** forms this ion at only $^1/_{20}$th the relative



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intensity under very similar spectrometer conditions. In all likelihood what is presumably the same (but much less abundant) peak derived from **11** is formed as the result of a molecule–ion interaction involving the unusually abundant peak *m/e* 141 ($C_6H_5SO_2^+$). The ready thermal decomposition which **11** undergoes, a property shared by most azo compounds, could be responsible for its observed facility in forming ion–molecule interaction products.

Finally, it must be mentioned that many of the fragment ions supporting the assigned azo structure of **11** are the same as those observed for the hydrazine **1**. However, it must also be emphasized that the large difference in the abundance of the *m/e* 142 ion (a factor of 20 under similar spectrometer conditions) eliminates the presence of the hydrazine as an impurity in any significant amounts, as does the absence of the 312 and P ions.

F. Other Lines of Evidence.—It seemed desirable to test the proposed structure of **11** by means of chemical reactivity studies. Efforts were made to reduce it to the parent hydrazine **1** without success. When **11** was subjected to hydrogenation with finely divided platinum or platinum on charcoal, at 3 atm in alcoholic solvent, the starting material was recovered unchanged. Evidently the bulky sulfonyl substituents on the azo center of unsaturation prevents its adsorption on the catalyst, the necessary preliminary step to heterogeneous hydrogenation.

The attempt to reduce **11** to **1** by purely chemical means, such as zinc in acid solution, failed to produce the desired reaction and resulted instead in products representing sulfone–nitrogen cleavage. The ir spectrum of this product mixture showed neither an N–H band at *ca.* 3430 cm^{-1} to identify the hydrazine, nor the —N=N— band at 1575 cm^{-1}, characteristic of the starting material. It is also clear from this result that the unsymmetrically substituted hydrazine **2** was not present in the complex reduction product obtained.

A further indication of the steric hindrance to reactivity of the azo group in **11** that is afforded by the bis sulfone substituents was realized in attempts to utilize it as a Diels–Alder dienophile. Analogous azobisdiformate esters have been shown to undergo reaction rather readily, using typical dienes such as cyclopentadiene. However, using reaction conditions (see Experimental Section) which usually yielded good conversions with azobisdiformates, the reaction of **11** with cyclopentadiene failed completely. The unconverted starting material was recovered nearly quantitatively.

To the best of our knowledge **11** is a new composition of matter and is the first example of a stable class of compounds possessing the azobisdisulfone structure. Further studies of the properties, methods of preparation and reactions of this class of substances are currently in progress in these laboratories.

Experimental Section

All melting points were taken with a Fisher-Johns hot-stage apparatus and are essentially uncorrected.

N,N′-Bisbenzenesulfonylhydrazine (**1**) was prepared according to the method of Hinsberg.[6] Recrystallization from glacial acetic acid gave white needles, mp 236–237° (lit.[5] *ca.* 245°).

Dibenzenesulfonimide (**4**).—Benzenesulfonyl chloride (1.1 mol) was added dropwise over a period of 2 hr to a solution of benzenesulfonamide (1.0 mol) in 880 ml of 5% NaOH in water. The pH of the reacting solution was maintained throughout at *ca.* 7.2 by discreet additions of 5% NaOH. When addition was completed, stirring was continued for 30 min and 100 ml of 40% NaOH run into the mixture. The charge was then stirred and cooled to 15° and the sodium salt of **4** permitted to precipitate under stirring. In various runs, between 0.6 and 0.9 mol of the sodium salt was obtained in several runs by filtration. After taking up in water, boiling, and cooling, a sample of the salt melted above 260° with decomposition. Addition of slightly more than 1 equiv of 36% HCl at 25° to a solution of 1 mol of sodium salt in 300 ml of H_2O gave the free imide **2**, which is nearly insoluble in water at pH 2. On recrystallization from ethanol–water solution, a white crystalline product was obtained, mp 157–159° (lit.[9] 157–158°).

N-Bromodibenzenesulfonimide.—A solution of 20 g of **4** (*ca.* 0.10 mol) in 4 g of NaOH and 30 ml of H_2O was cooled by addition of 20 g of ice. The flask was surrounded by an ice bath and under vigorous (magnetic) stirring 6 ml of bromine was added all at once. Stirring was continued for 5 min longer and the precipitate collected on a fritted-glass filter. It was washed with cold water until free of bromide. The product (25-g yield) after drying in a desiccator at 40° melted at 120–122°.

Anal. Calcd for $C_{12}H_{10}S_2O_4NBr$: Br, 21.27; Found: Br, 20.34.

The infrared spectrum showed no N–H bands in the characteristic frequency regions.

Attempted Preparations of N-Nitrosodibenzenesulfonimide.—The experiments are summarized in Table I.

Di(phenylsulfonyl)diimide.—A solution of 0.2 g of **1** in 25 ml of ethanol was brought to reflux with stirring and 3 ml of bromine was added dropwise over 1 hr. Reflux was continued for 1 hr after addition was completed. The reflux condenser was then removed and the solvent permitted to boil away until the volume wa reduced to less than 5 ml. When a few drops of water was added to the cooled residue, a crystalline product separated, mp 188–193°. On recrystallization from ethanol–H_2O, the pure product resulted, mp 193–194° with fuming and decomposition. Upon infrared analysis (KBr pellet) of the product, the most characteristic band was observed at 1575 cm^{-1} (—N=N—).

Anal. Calcd for $C_{12}H_{10}N_2S_2O_4$: C, 46.15; H, 3.20; N, 8.97; S, 20.51; O, 21.07. Found: C, 46.21; H, 3.12; N, 8.92; S, 20.31; O, 21.04.

Reaction of N-Bromodibenzenesulfonimide in Liquid Ammonia.—Anhydrous liquid NH_3 (100 ml) was introduced into a 500-ml, three-necked flask equipped with mechanical stirrer and a Dry Ice condenser. Freshly cut sodium (4.72 g) was converted into sodamide in the usual fashion through use of a small amount of ferric nitrate. When the blue color had disappeared, the N-bromodibenzenesulfonimide (35.0 g) was added portionwise. After addition was completed, the mixture was stirred for 6 hr, the cooling condenser was removed, and the excess ammonia was vented. On working up the residue only dibenzenesulfonimide could be isolated.

N,N′-Bis-*p*-toluenesulfonylhydrazine (**1a**) was prepared according to the directions of Jennings.[5] Recrystallization from acetone–water solution afforded a product of mp 217–218° as white needles (lit.[5] 219–220°).

Reduction of 11.—A solution of 0.2 g of **11** in 15 ml of ethanol was charged in a round-bottom, three-necked flask equipped with reflux condenser and magnetic stirrer. To this was added in small portions at 30–40° powdered zinc (0.1 g, total) and concentrated HCl (4 ml, total) allowing sufficient time between additions of both of these reagents for foaming to subside. After addition was completed, the temperature was raised to reflux and held there for 0.5 hr. The solution was now cooled and filtered, and the solvent was stripped under reduced pressure,

leaving a viscous liquid residue which resisted repeated attempts at crystallization. The ir spectrum of this residue showed neither a band at *ca.* 3430 nor at 1575 cm^{-1}, and thus contained neither **1** or **11** in significant amounts.

Attempted Condensation of 11 with Cyclopentadiene.—A solution of 0.6 g (*ca.* 0.002 mol) of **11** and 0.150 g (*ca.* 0.002 mol) of freshly prepared cyclopentadiene in anhydrous ether was maintained at 15–20° for 24 hr under nitrogen with magnetic stirring.[3] Upon stripping all volatiles at the water pump up to steam bath temperatures slightly more than 0.6 g of a solid remained which had an ir spectrum nearly identical with that of the starting compound **11**.

Mass Spectra.—That of N,N′-bis-*p*-toluenesulfonylhydrazine was taken on an Atlas double focus high resolution instrument (Atlas Mess and Analysentechnik GMBH Bremen) through the courtesy of Dr. C. Djerassi at Stanford University, Stanford, California, while one of us (H. K.) was in residence as visiting professor of Chemistry in 1964. Direct introduction of the sample was possible with this instrument and consequently pyrolytic decomposition could be avoided. The spectra of N,N′-bisbenzenesulfonylhydrazine and of compound **11** were recorded under conditions specified in Table II through the courtesy of Dr. W. B. Askew, for which we are most grateful.

Nmr spectra were determined with either a Varian A-60 or Varian HR-100 instruments.

H bonding data were taken with a Perkin-Elmer Model 337 grating infrared spectrometer.

pK_a measurements were obtained by use of a Sargeant Model D recording titrator.

Ebullioscopic determinations of the molecular weight of **11** were carried out in benzene solution with benzyl as a standard and using an instrumental design described in the literature.[13] Four determinations were made with the results ranging from 298–299, compared to calculated 310.

Registry No.—**1**, 6272-36-2; **3**, 98-10-2; **4**, 2618-96-4; **11a**, 15815-54-0; **11b**, 15815-55-1; N-bromodibenzenesulfonimide, 15815-56-2.

(13) R. V. Bonnar, M. Dimbal, and F. H. Strass, "Number Average Molecular Weight," Interscience Publishers, Inc., New York, N. Y., 1958.

The Hydrohalogenation and Deuteriohalogenation of 7-Norbornenone

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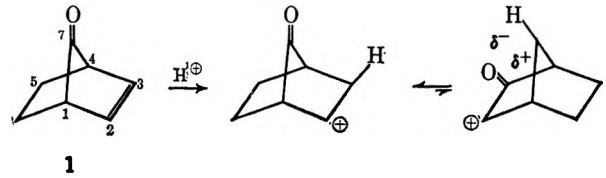
The polar addition of hydrogen bromide, hydrogen chloride, and the corresponding deuterio halides to 7-norbornenone (**1**) has been carried out. The products cannot be reconciled with an intermediate involving interaction between the protonated carbonyl group and the π electrons of the ethylenic system. The major product is the result of *cis–exo* addition with the rearranged *exo* product occurring to a much smaller extent. The importance of steric, bridging, and torsional effects in controlling the stereochemistry are considered.

The stereochemistry of the electrophilic addition of hydrogen halides to olefins has received considerable attention.[1–8] It has become apparent that the *trans* addition of a hydrogen halide to an α,β-unsaturated carboxylic acid is the result of a 1,4 addition and is not related mechanistically to the reaction of an isolated olefin.[9] It has also become apparent that the stereochemical course of addition to an isolated olefin is not a simple function of π complexes and steric effects. The occurrence of ion pairs or complexes leading to a preference for *cis* addition, unless torsional strain effects are unfavorable, is now recognized.[3,7]

The norbornene system has occupied a place by itself in these investigations owing to the importance, if any, of the delocalized "nonclassical" carbonium ion or the "windshield wiper effect"[10] in determining the stereochemistry of electrophilic additions. Steric effects alone cannot account for all of the *exo* products[2,4,5] since the hydrochlorination of bornylene and apobornylene also produces *exo* adducts.[6] The occurrence of a delocalized structure in the transition state of the proton-addition step also seems unlikely in view of the recent results of Brown[6] and Schleyer.[7]

We have investigated the hydrohalogenation, and deuteriohalogenation, of 7-norbornenone (**1**) in the hopes that we would be able to examine the stereochemical course of addition when a classical secondary norbornyl cation was involved. Attack of a proton on the double bond of 7-norbornenone (**1**) should produce a carbonium ion which is reluctant to rearrange as the rearranged carbonium ion involves a juxtaposition of positive changes. Likewise delocalization of the σ electrons of the C-1, C-6 bond in the transition state of



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the proton-addition step would seem less important here as compared to the norbornyl cation. If this is true, then it is possible that neither the nonclassical carbonium ion nor the equilibrating classical ions would be involved in the product-controlling attack of the halide ion.

Results

The polar hydrobromination, and deuteriobromination, of 7-norbornenone (**1**) was carried out in methylene chloride saturated with hydrogen bromide, or deuterium bromide, at 0°. The reaction was complete within

(1) P. K. Freeman, F. A. Raymond, and M. F. Grostic, *J. Org. Chem.*, **29**, 1625 (1964).

(2) S. J. Cristol, J. C. Morrill, and R. A. Sanchez, *ibid.*, **31**, 2719, 2726, 2733, 2738 (1966), and previous papers; S. J. Cristol and R. Caple, *ibid.*, **31**, 2741 (1966).

(3) M. J. S. Dewar and R. C. Fahey, *Angew. Chem., Intern. Ed. Engl.*, **3**, 245 (1964), and references cited therein.

(4) H. Kwart and J. L. Nyce, *J. Amer. Chem. Soc.*, **86**, 2601 (1964).

(5) J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *ibid.*, **88**, 4922 (1966).

(6) H. C. Brown and K.-T. Liu, *ibid.*, **89**, 466, 3898, 3900 (1967), and references cited therein.

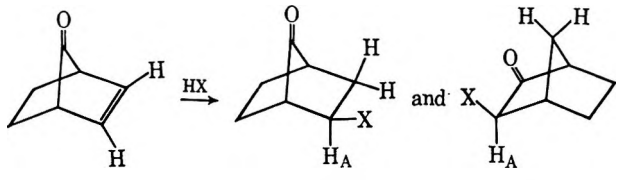
(7) P. von R. Schleyer, *ibid.*, **89**, 3901 (1967).

(8) R. C. Fahey, *Chem. Commun.*, **18**, 936 (1967), and previous papers.

(9) R. Caple, and W. R. Vaughan, *Tetrahedron Lett.*, 4067 (1966), and references cited therein.

(10) H. C. Brown, Abstracts, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 21, 1961, p 2-O; "Non-Classical Intermediates," Organic Reaction Mechanisms Conference, Brookhaven, N. Y., Sept 5, 1962.

15 hr, and the crude adducts were recovered in 85% yields. The polar hydrochlorination in methylene chloride of this deactivated olefin however was very slow, less than 10% in 7 days at 0°, and the addition was carried out using 37% hydrochloric acid. The aqueous solution for the deuteriochlorination was generated by hydrolyzing dichlorodimethylsilane.[11] The mixtures were shaken vigorously for *ca.* 48 hr, and the adducts were recovered by extraction in 55–65% yields. Product analyses were made by nuclear magnetic resonance (nmr) and vapor phase chromatographic (vpc) techniques.

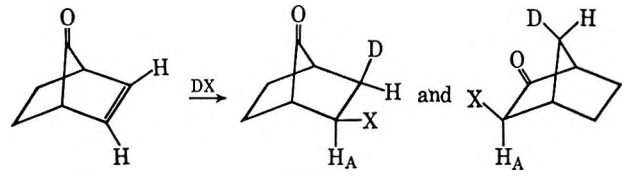


1 2, X = Br 4, X = Cl 3, X = Br 5, X = Cl

Only two major products in the ratio of 85:15 were observed in the hydrobromination of 7-norbornenone (**1**). These products are the unrearranged *exo* hydrobromide **2** and the rearranged *exo* adduct **3**. No other adducts could be detected by thin layer chromatography, vpc, or by nmr. This product ratio does not change as the reaction time is reduced, the same ratio of **2**/**3** being observed at 40% reaction. Furthermore, an authentic sample of *exo*-3-bromonorcamphor (**3**) is stable under the reaction conditions. The presence of hydroquinone also does not alter the product distribution. It is felt, therefore, that kinetically controlled adducts resulting from a polar addition are being observed. Essentially the same product ratio is obtained when the addition is carried out in 48% hydrobromic acid although the per cent recovery was only 50%.

The configurational assignments for **2** and **3** were made by nmr.[12] The signal for H_A in *exo*-2-bromo-7-norbornanone (**2**) occurs as a triplet, J = 5.8 cps, at δ 4.3. This multiplet is consistent with the assigned configuration[13–15] where $J_{obsd} = {}^1/_2$ (J_{cis} and J_{trans}) and where there is no detectable coupling with the bridgehead hydrogen. This averaging effect for J_{cis} and J_{trans} is confirmed in the nmr analysis of the deuterio bromide discussed shortly. The signal for H_A in *exo*-3-bromonorcamphor (**3**) occurs as a doublet, J = 3.0 cps, at δ 3.8 with finer splitting being less than 0.5 cps. This is in agreement with the reported spectrum for **3**[16] and a spectrum obtained by us on an authentic sample.

The addition of deuterium bromide confirms the *cis–exo* nature of the addition to produce **2**. The triplet for H_A in **2** collapses to a clean doublet in **6**, J_{cis} = 8.8 cps. This is the value expected for a *cis–endo* vicinal coupling[17] and confirms the nature of the "deceptively simple spectrum" of the *endo* hydrogen H_A in **2** as described by Flautt and Erman.[13,18] The multiplet for H_A in **7** is unchanged as one would predict for deuterium at the *syn*-C-7 position.

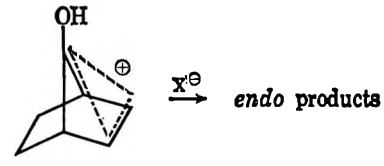


1 6, X = Br 8, X = Cl 7, X = Br 9, X = Cl

The results from the hydrochlorination are similar. The *exo* hydrochlorides, **4** and **5**, are obtained in a ratio of 93:7. The product ratio again does not vary even when the reaction is carried to 13% completion in 19% hydrochloric acid. The multiplet for H_A in **4** is again a "deceptively simple" triplet, J = 4.6 cps, at δ 4.2. The triplet collapses to a doublet, J = 8.5 cps, in the labeled adduct **8**.

Discussion of Results

It was initially hoped that appreciable *endo* products would be observed in the hydrohalogenation of 7-norbornenone (**1**). An *endo* isomer conceivably could result from the interaction between the protonated carbonyl group and the π electrons of the double bond. It has recently been shown by nmr studies that such an interaction can occur leading to the delocalized structure **10**.[19] There is also some indication, LCAO–MO calculations and ultraviolet data,[20] for an interaction of the π-carbonyl system of 7-ketonorbornene (**1**) with the π-ethylenic system although the sodium borohydride reduction of this ketone does not involve delocalization.[21] Likewise the products observed in this study are not derived from the protonated structure **10**.



10

The hydrohalides are consistent with those derived from *exo* protonation of the carbon–carbon double bond in **1**. Attempts to promote interaction between the π systems of **1** by catalyzing the addition with aluminum bromide or aluminum chloride lead to increased polymerization and no detectable change in the product distribution.

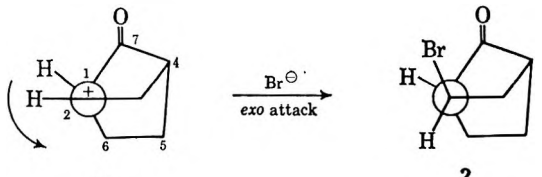
The *exo*/*endo* product ratios observed in this investigation differ from those observed in solvolysis studies.[22–24] These differences are expected[6] owing to the presence of intimate ion pairs in the solvolysis work. Thus the acetolysis of the *endo*- and *exo*-7-ketonorbornyl tosylates produces considerable *endo*

(11) W. H. Greive and K. F. Sporek, *J. Chem. Educ.*, **43**, No. 7, 381 (1966).
(12) Chemical shifts are relative to tetramethylsilane on 60-Mc instrument.
(13) T. J. Flautt and W. F. Erman, *J. Amer. Chem. Soc.*, **85**, 3212 (1963).
(14) A. L. Thomas, R. A. Schneider, and J. Meinwald, *ibid.*, **89**, 68 (1967).
(15) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 216 (1961).
(16) J. Meinwald, Y. C. Meinwald, and T. N. Baker, *J. Amer. Chem. Soc.*, **85**, 2513 (1963).
(17) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).
(18) For other examples, see ref 14.
(19) S. Winstein, *Chem. Eng. News*, 54 (April 3, 1967).
(20) E. I. Snyder and B. Franzus, *J. Amer. Chem. Soc.*, **86**, 1166 (1964).
(21) H. C. Brown and J. Muzzio, *ibid.*, **88**, 2811 (1966).
(22) P. G. Gassman and J. L. Marshall, *ibid.*, **88**, 2822 (1966); *ibid.*, **87**, 4648 (1965).
(23) P. G. Gassman and J. L. Marshall, *Tetrahedron Lett.*, No. 46, 4073 (1965).
(24) M. Hanack and J. Dolde, *ibid.*, No. 3, 321 (1966).

acetates but no rearranged acetates[22,23] owing to the early coordination of acetic acid with the developing ion pair.

The formation of the unrearranged hydrohalide as the primary product supports the classical character of the 7-ketonorbornyl cation **11**.[22,23] The extent to which rearrangement does occur would seem to be more consistent with the relief of angle strain involved in placing the trigonal carbonyl carbon in the ethylene bridge than with a nonclassical intermediate involving a partial delocalization of the C-1, C-6 σ electrons. The internal angle at C-7 is about 96.5° compared to about 104° at C-2.[25] Although the observed major *cis-exo* adduct can be explained in this system as being derived from a transfer to the least-hindered side of the double bond, it must be emphasized that hydrogen chloride also adds to bornylene and apobornylene to yield *exo* adducts.[6] Furthermore, the concerted four-centered addition mechanism for the electrophilic addition of hydrogen chloride to certain norbornene systems has recently been considered to be less likely than a mechanism involving a carbonium ion intermediate.[6] If similar considerations are applicable here, the *exo* approach of the proton and the *exo* approach of the halide ion, as a complex with hydrogen halide, are probably independent steps although the stereochemical control of approach may be governed by a common factor.

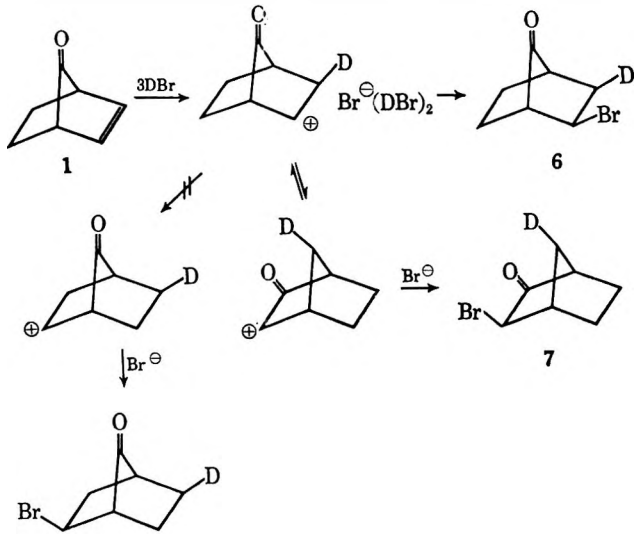
An alternate explanation to account for the stereochemistry is the torsional strain factor. Similar interpretations have been used to explain why, although there is preference for *cis* addition of a hydrogen halide,[3] in certain olefins the *trans* addition product is the major adduct.[26-28] Both steps in the addition involve a conversion of a sp^2-hybridized carbon into a sp^3-hybridized carbon. Approach from the *exo* side proceeds with relief of torsional strain in the transition state as compared to *endo* approach where eclipsing will occur between the bridgehead carbon–hydrogen bond and the adjacent carbon–hydrogen bond on the ethylene bridge. The importance of torsional effects in controlling the stereochemistry of attack in norbornane derivatives has recently been discussed by Schleyer.[25] The effect is indicated by the *exo* attack of bromide ion on the 7-ketonorbornyl cation **11** to produce **2**.



11 **2**

The stepwise addition of deuterium bromide to 7-norbornenone (**1**) is outlined in Scheme I. The mechanism is consistent with the other known facts concerning the electrophilic addition of a hydrogen halide to an olefin.[3,30-32] It must be pointed out that the clean collapse of the triplet for the proton on the carbon-bearing bromine upon addition of deuterium bromide means that a 6,2-hydride shift must be occurring to an undetectable extent.

SCHEME I
FLOW DIAGRAM FOR THE ELECTROPHILIC ADDITION OF DBr TO 1



Experimental

Materials.—7-Norbornenone (**1**) was synthesized by the oxidation of bicyclo[2.2.1]hept-2-en-*anti*-7-ol[33] according to the procedure of Bly.[34] Deuterium bromide was generated by the addition of deuterium oxide, 99.8% (Columbia Organic Chemicals Co., Inc.) to Eastman phosphorus tribromide. The deuterium bromide was trapped and distilled into reagent methylene chloride from a Dry Ice–acetone trap. An aqueous solution of deuterium chloride was formed by the hydrolysis of dichlorodimethylsilane (Dow Chemical Co.) according to the procedure of Greive and Sporek.[11] The aqueous solution of approximately 20% deuterium chloride was removed and separated from the polymeric silicone oil layer by means of a syringe.

Analytical.—Nuclear magnetic resonance spectra were obtained using a Varian Associates Model A-60 spectrometer using tetramethylsilane as an internal standard. Gas chromatographic analyses were performed on an Aerograph A90-P3 instrument using 20% silicone GE (5 ft × 0.25 in.), 20% Carbowax 20M (10 ft × 1/8 in.), and 10% fluorosilicone QF-1 (5 ft × 0.25 in.) columns. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Addition of Hydrogen Bromide to 7-Norbornenone (1).—7-Norbornenone (**1**), 2.9 g (27 mmol), was dissolved in 200 ml of reagent methylene chloride and saturated with anhydrous hydrogen bromide (Matheson Co., Inc.) at 0° in a bubbler trap. The acid solution was tightly stoppered and allowed to stand for 36 hr at 0°. After the addition, the excess hydrogen bromide and methylene chloride were removed by gentle heating on a hot plate. Fresh methylene chloride was added, and the solution was dried over anhydrous magnesium sulfate. Removal of the solvent under vacuum yielded 4.3 g (85%) of hydrobromides and no starting ketone as indicated by nmr and vpc. The retention times on the fluorosilicone column at 125° were 14 and 18 min for the minor and major hydrobromides, respectively. The retention time of the minor adduct was indistinguishable from a sample of *exo*-3-bromonorcamphor (**3**) obtained by the bromination of norcamphor (Aldrich Chemical Co.). The purified product ratio was essentially identical with the original as indicated by both nmr and vpc. Shorter runs and the addition of deuterium bromide were carried out in a similar fashion. Attempts to separate the adducts by preparative vpc were unsuccessful owing to the thermal instability under autoprep conditions (Aerograph A-700, silicone SE-30 (20 ft × 1/8 in.),

(25) P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964).
(26) G. S. Hammond and T. D. Nevitt, *ibid.*, **77**, 1594 (1955).
(27) J. V. Smirnov-Zamkov and G. A. Piskovitina, *Ukr. Khim. Zh.*, **28**, 531 (1962).
(28) R. C. Fahey and R. A. Smith, *J. Amer. Chem. Soc.*, **86**, 5935 (1964).
(29) P. von R. Schleyer, *ibid.*, **89**, 701 (1967).
(30) P. B. D. de la Mare and R. Boulton, "Electrophilic Additions to Unsaturated Systems," Elsevier Publishing Co., New York, N. Y., 1966.
(31) B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms, 1965," John Wiley and Sons, Ltd., London, 1966, p 104 ff.
(32) K. Fukui, *Bull. Chem. Soc. Jap.*, **39**, 498 (1966).
(33) P. Story, *J. Org. Chem.*, **26**, 289 (1961).
(34) R. K. Bly and R. S. Bly, *ibid.*, **28**, 3165 (1963).

195°). These additional unidentified decomposition products could readily be detected by nmr and by vpc under the analytical conditions given above.

Anal. Calcd for C_7H_9BrO: C, 44.47; H, 4.80; Br, 42.27. Found: C, 44.69; H, 5.00; Br, 42.32.

Addition of Hydrogen Chloride to 7-Norbornenone (1).—To 7-norbornenone (1), 3.0 g (28 mmol), in a test tube was added 40 ml of concentrated (37%) hydrochloric acid. The tube was sealed and shaken vigorously for 48 hr at room temperature. The tube was opened and extracted with two 100-ml portions of ethyl ether. The ethereal extracts were combined and washed well with water and dried over anhydrous magnesium sulfate. The ether was removed under vacuum, and the dark residue was distilled to yield 2.3 g (58%), bp 52–56° (0.4 mm). Partial additions were carried out in 19% hydrochloric acid and shorter reaction times. The addition of deuterium chloride as a 20% solution in deuterium oxide was carried out in 9 days. As with the hydrobromides the major adduct was unstable under autoprep conditions. The retention times on a 5-ft QF-1 fluorosilicon column were 8.5 and 12 min for the minor and major adducts, respectively.

Anal. Calcd for C_7H_9ClO: C, 58.14; H, 6.28; Cl, 24.52. Found: C, 57.94; H, 6.42; Cl, 24.74.

Acknowledgments.—We are indebted to the Research Corporation and the Graduate School of the University of Minnesota for support of this work.

The Stereochemistry of Acyl Halide Addition to Olefins. The Intramolecular Cyclization of Cyclooct-4-*cis*-ene-1-carboxylic Acid Chloride

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Received September 21, 1967

The intramolecular cyclization of cyclooct-4-*cis*-ene-1-carboxylic acid chloride (1) proceeds by *cis* addition to produce 2-*exo*-chlorobicyclo[3.3.1]nonan-9-one (2) as the principal product in a variety of solvents and in the absence of added Lewis acid catalysts. In the presence of catalytic quantities of aluminum chloride, the addition proceeds predominantly *trans* to produce 2-*endo*-chlorobicyclo[3.3.1]nonan-9-one (3) as the major product. Under more polar conditions (*e.g.*, 5% solution of boron trifluoride etherate in diglyme), cyclization occurs with loss of hydrogen chloride to produce principally bicyclo[3.3.1]non-2-en-9-one (4). These results are compared with the course of hydrogen halide addition to olefins. Structure elucidation of the chloro ketones 2 and 3 was based upon spectral analysis, X-ray crystal analysis, and the contrasting behavior of each isomer to base. In refluxing methanolic potassium hydroxide the *exo* isomer 2 undergoes elimination to bicyclo[3.3.1]non-2-en-9-one (4), while the *endo* isomer 3 suffers fragmentation to the potassium salt of cyclooct-4-ene-1-carboxylic acid (6).

Although limited examples of the Friedel–Crafts addition of acid chlorides to olefins to produce chloro ketones can be cited, knowledge of the stereochemistry of these additions is completely lacking.[1] In the examples studied, either the stereochemistry of the chloro ketone products was not determined, or the structure of the products was not amenable to stereochemical elucidation.[1] Indeed, stereochemical resolution of the chloro ketone products from the addition of acid chlorides to simple acyclic or cyclic systems may be inconclusive, since the initially formed products would probably undergo rapid enolization and epimerization under the conditions employed for the reaction. For this reason we chose to investigate the intramolecular cyclization of cyclooct-4-*cis*-ene-1-carboxylic acid chloride (1). Intramolecular addition of the acid chloride function to the olefin function of 1 would produce a bicyclic ketone which could not undergo enolization. If cyclization of 1 could be effected without loss or epimerization of the chloride function from the initially produced chloro ketone, the stereochemistry of addition could be ascertained at least for this system.

Results

We were able to find reaction conditions for cyclization of 1 which stereoselectively produced either 2-*exo*-chlorobicyclo[3.3.1]nonan-9-one (2) (*cis* addition) or 2-*endo*-chlorobicyclo[3.3.1]nonan-9-one (3) (*trans* addition) without epimerization of the initially produced chloro compound or prevalent dehydrohalogenation. It is noteworthy that bicyclo[4.2.1]nonane derivatives (*i.e.*, 5a and 5b), which would have been formed by the converse addition of acid chloride to the olefin moiety, were not produced under these conditions.[2,3]

In initial experiments, treatment of a 5% solution of 1[4] in 5% boron trifluoride etherate–diglyme at 100° effected cycloaddition of the acid chloride function but with almost complete loss of hydrogen chloride. Thus, bicyclo[3.3.1]non-2-en-9-one (4), the structure of which was verified by comparison with an authentic sample,[5] was produced in 53% yield while only small quantities of the chloro compounds 2 (5%) and 3 (3%) were formed under these conditions. An appreciable quantity (10%) of methyl cyclooct-4-*cis*-ene-1-carboxylate was also produced, undoubtedly by esterification of methanol (generated by acid cleavage of the diglyme) with the acid chloride 1. When the acid chlo-

(1) (a) For a review of acyl halide additions to alkenes, see G. A. Olah, Ed., "Friedel–Crafts and Related Reactions," Vol. I, Interscience Publishers, John Wiley and Sons, Inc., New York, N. Y., 1963, pp 129–133; (b) H. Wieland and L. Bettag, *Ber.*, **55**, 2246 (1922); (c) J. R. Catch, D. F. Elliot, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 278 (1948), and references cited therein; (d) R. H. Carroll and G. B. L. Smith, *J. Amer. Chem. Soc.*, **55**, 370 (1933); (e) E. M. McMahon, J. N. Roper, Jr., W. P. Utermohlen, Jr., R. H. Hasek, R. C. Harris, and J. H. Brant, *ibid.*, **70**, 2971 (1948); (f) J. Colonge and K. Mostafavi, *Bull. Soc. Chim. Fr.*, (5), **6**, 335, 342 (1939).

(2) In this regard, it is interesting to compare the cyclization of 1 with the solvolysis of cyclooct-4-ene-1-methanol derivatives. Under conditions of kinetic control, bicyclo[3.3.1]nonane derivatives are produced almost exclusively from this latter solvolysis reaction.[3] Under more vigorous conditions, the initially produced bicyclo[3.3.1]nonane derivatives are apparently equilibrated to significant quantities of bicyclo[4.2.1]nonane compounds.[3a]

(3) (a) W. Kraus, W. Rothenwöhrer, W. Kaiser, and M. Hanack, *Tetrahedron Lett.*, 1705 (1966); M. Hanack and W. Kaiser, *Angew. Chem.*, **76**, 572 (1964); *Angew. Chem., Intern. Ed. Engl.*, **3**, 583 (1964); (b) A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *J. Amer. Chem. Soc.*, **87**, 3130 (1965); (c) H. Felkin, G. LeNy, C. Lion, W. D. K. Macrosson, J. Martin, and W. Parker, *Tetrahedron Lett.*, 157 (1966); (d) K. H. Baggaley, J. R. Dixon, J. M. Evans, and S. H. Graham, *Tetrahedron*, **23**, 299 (1967).

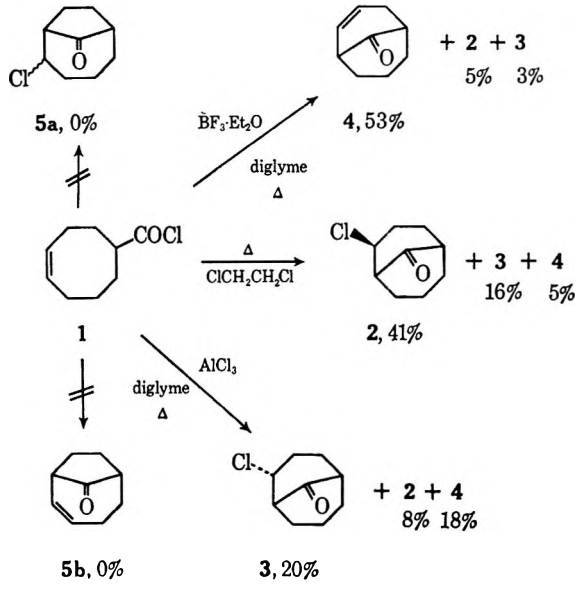
(4) (a) Prepared in 86% yield by treatment of cyclooct-4-*cis*-ene-1-carboxylic acid[4b] with oxalyl chloride; (b) K. Ziegler and H. Wilms, *Ann.*, **567**, 1 (1950).

(5) C. S. Foote and R. B. Woodward, *Tetrahedron*, **20**, 687 (1964).

ride was heated at 83–84° in ethylene dichloride solution for 16 hr in the absence of an added catalyst, *exo*-2-chlorobicyclo[3.3.1]nonan-9-one (**2**) was the principal product of the cyclization reaction. The latter ketone, produced in 41% yield, was accompanied by the *endo* isomer **3** (16%) and a small quantity of the olefinic ketone **4** (5%). When benzene, monoglyme, trichloroethane, or acetic acid was employed as solvent, the yields of products **2**, **3**, and **4** were decreased, but the ratio of olefin/*exo* isomer **2**/*endo* isomer **3** was not altered significantly (see Experimental Section). The remaining products were dimeric or polymeric in nature. An appreciable quantity of methyl cyclooct-4-*cis*-ene-1-carboxylate also was produced when monoglyme or diglyme was employed as solvent.

On the other hand, treatment of **1** with catalytic quantities of aluminum chloride in monoglyme or diglyme at 88 and 100°, respectively, for 16 hr afforded the *endo* epimer **3** as the principal product (20–26%). The *exo* epimer **2** was produced in 6–8% yield and the olefin **4** in 18–19% yield. Products of intermolecular condensation were increased in the presence of aluminum chloride catalyst.

The following two experiments established that the ketone **3** was produced directly from the acid chloride **1** and not by aluminum chloride catalyzed epimerization of **2** or by addition of hydrogen chloride to the olefin **4**. These experiments also indicate that the olefin **4** was produced directly from **1** and not by aluminum chloride catalyzed dehydrohalogenation of **2**.



(1) When a solution of the *exo*-chloro epimer **2** was heated in benzene or in diglyme with aluminum chloride (see Experimental Section), starting ketone **2** was recovered in 77 and 84% yields, respectively. Only trace amounts of the olefin **4** and no detectable quantities of the epimeric chloro ketone **3** were observed under these conditions. (2) Treatment of the olefin **4** with aluminum chloride under the same conditions in the absence or presence of added hydrogen chloride led to 93 and 91% recoveries of starting olefin, respectively. The chloro ketones **2** and **3** were produced in 0.4 and 2%, respectively, from the latter reaction but were accompanied by at least four other isomeric chloro ketones, produced in 2, 2, 1, and 0.3%, respectively. Since the reaction product from the cyclization of **1** is devoid of these latter chloro ketones, the probability that even a small portion of the *endo* isomer **3** is produced from the olefin **4** under the conditions described here seems remote.

Structure Elucidation of Ketones 2 and 3. Mass spectral data and elemental analyses established the empirical formula $C_9H_{13}OCl$ for the two cyclization products **2** and **3**. The infrared spectra of ketones **2** and **3** displayed carbonyl absorption at 5.79 and 5.78 μ, respectively, in excellent agreement with the values 5.80 and 5.77 μ recorded for the parent bicyclo[3.3.1]-nonan-9-one[5] and bicyclo[3.3.1]non-2-en-9-one[5] structures, respectively. In contrast, the 2-chlorobicyclo-[4.2.1]nonan-9-one epimers (**5a**), which might have resulted from reverse addition of the acid chloride to the olefin, should show absorption at no greater than 5.72–5.75 μ for a nonstrained five-membered ring ketone.[6-9]

The basic ring skeleton and the positions and stereochemistry of the chloro functions in **2** and **3** were implied from the characteristic behavior of each isomer to base. The epimer **3**, on treatment with refluxing 2 *M* methanolic potassium hydroxide, suffered cleavage to potassium cyclooct-4-*cis*-ene-1-carboxylate[10] (87%) and potassium cyclooct-3-*cis*-ene-1-carboxylate[10] (4%). In contrast, under the same conditions, the epimer **2** underwent dehydrochlorination to the olefin **4**. The fragmentation of **3** to **6** is apparently rapid compared to the dehydrochlorination of **2** to **4**. Thus, a mixture of **2** and **3** on treatment with potassium *t*-butoxide in wet *t*-butyl alcohol at room temperature led to quantitative fragmentation of **3**, while the epimer **2** was recovered unchanged. In fact, the latter treatment represents an excellent procedure for isolation of the *exo* epimer free of the *endo* isomer.

That the fragmentation product **6** was produced directly from **3** and not from the olefin **4** (which might have been formed by initial dehydrochlorination of the conformer **3b**) was confirmed by the observed stability of **4** to the same basic conditions. Thus, the olefin **4**, after treatment for 16 hr with refluxing 5 *M* methanolic potassium hydroxide was recovered unchanged.[11,12]

The remarkable ease with which the *endo*-chloro ketone undergoes ring scission can be interpreted as an exemplification of the general rule that fragmentation reactions proceed with greatest facility when the bonds

(6) Thus the parent bicyclo[4.2.1]nonan-9-one[7,8] and the isomeric 7-methylbicyclo[4.2.1]nonan-9-ones[8] display carbonyl absorption at 5.75 μ, the 1-methyl and 1,5-dimethyl derivatives[8] at 5.73 μ, and the 2-methyl derivative[8] at 5.72 μ.

(7) C. D. Gutsche and T. D. Smith, *J. Amer. Chem. Soc.*, **82**, 4067 (1960).

(8) G. Opitz and H. Mildenberger, *Ann.*, **650**, 115 (1961).

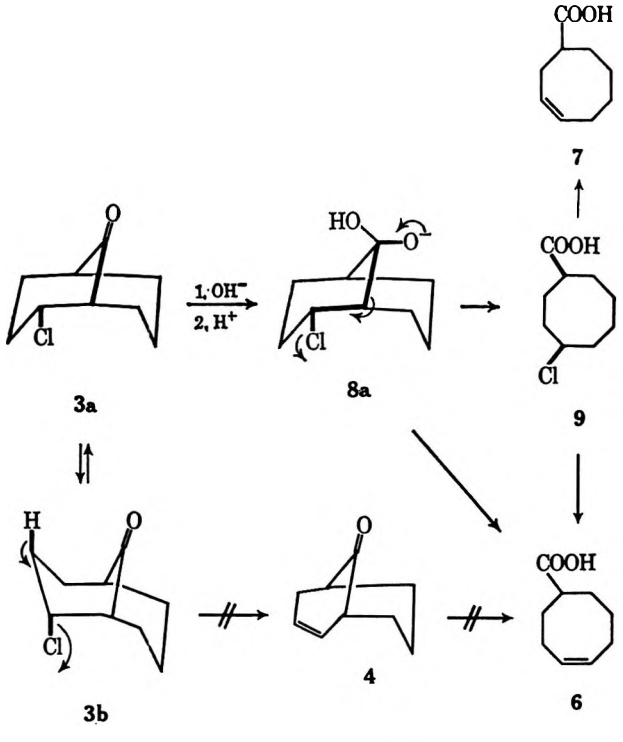
(9) C. D. Gutsche and J. E. Bowers, *J. Org. Chem.*, **32**, 1203 (1967).

(10) Isolated after acidification as the free acids **6** and **7**, respectively, and identified as the methyl ester derivatives. The esters were compared to authentic specimens, the syntheses of which are described by W. F. Erman and H. C. Kretschmar, *J. Amer. Chem. Soc.*, **89**, 3842 (1967).

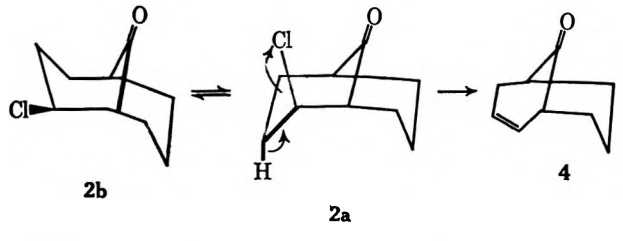
(11) Facile bridge fission seems to be a characteristic property of bicyclo-[3.3.1]nonan-9-ones containing an easily eliminated functional group in the 2-*endo* position.[12] In contrast, 2-*exo*-substituted bicyclo[3.3.1]nonan-9-ones undergo elimination to produce the corresponding bicyclo[3.3.1]non-2-en-9-ones apparently at a slower rate than the bridge fission of the corresponding 2-*endo* isomers.[12]

(12) (a) J. Martin, W. Parker, and R. A. Raphael, *J. Chem. Soc.*, 289 (1964); (b) G. L. Buchanan and G. W. McLay, *Tetrahedron*, **22**, 1521 (1966).

being broken are approximately parallel and coplanar.[13] In the chair conformation (**3a**) of the *endo*-chloro isomer the C-1,9 bond and the equatorial C–Cl bond are perfectly parallel and coplanar. The initially produced intermediate anion **8a**, then, would be expected to collapse readily to the acid **6**. The production of a small quantity of the cyclooct-3-*cis*-en-1-carboxylic acid (**7**) could be explained by a competitive protonation at C-1 concerted with bond scission to produce the intermediate chloro acid **9**. This acid could then undergo elimination to **6** and **7**. The collapse of **8a** to **6** apparently is a lower energy process than elimination of HCl from the boat conformer **3b**.



Even when the *exo* epimer **2** assumes a boat conformation (**2b**) the equatorial C–Cl bond is not coplanar with the C-1,9 bond, and fragmentation would not be anticipated. On the other hand, when **2** assumes the chair conformation **2a**, the axial C–Cl bond is ideally oriented for *trans*-diaxial elimination.[14]



Final confirmation of the structure **2** was made by X-ray diffraction. Webb and Becker[15] have shown that monoclinic needles of this isomer exist in the twin-chair conformation.[16,17] That the two epimers **2** and **3** also show preference for the twin-chair conformation in solution was indicated from the infrared C–H stretching frequency and nmr spectrum of each.

Fully saturated bicyclo[3.3.1]nonane compounds exhibit abnormal C–H stretching frequencies in the region of 2985–2995 cm^{-1} ascribed to interaction of the C-3 and C-7 *endo*-hydrogen atoms of the twin-chair conformer of the bicyclo[3.3.1]nonane skeleton.[3a,17a,b] In correspondence, the isomers **2** and **3** show C–H stretching frequencies at 2995 and 2985 cm^{-1}, respectively.

In the nmr spectrum of the *exo*-chloro ketone **2**, the C-2 proton appears at τ 5.46 as a multiplet of total band width 10.5 Hz, typical of an equatorial proton of a cyclohexane in the chair conformation.[12b,18] In the nmr spectrum of the *endo*-chloro ketone **3**, the C-2 proton appears as a multiplet of greater total band width (24 Hz)[12b,18] and at higher field (τ 5.78)[12b,19] as expected for an axial proton of a cyclohexane in the chair conformation. By decoupling the C-1 proton, apparent splittings of 4.9 and 12.0 Hz were determined for J (C-2–H, C-3–*exo* H) and J (C-2–H, C-3–*endo* H), respectively, in agreement with the assigned structure.[12b,18,20] An apparent splitting of 5.2 Hz for J (C-2–H, C-3–*exo* H) and J (C-2–H, C-3–*endo* H) was in accord with the equatorial assignment for the C-2 proton in structure **2**.[12b,18,20]

Discussion

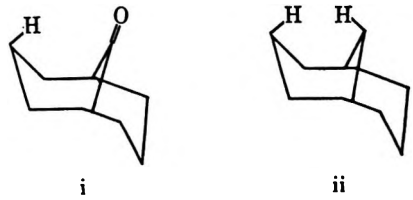
The mode of cycloaddition of the acid chloride **1** is reminiscent of the ionic addition of hydrogen bromide to aryl-substituted olefins.[21] Dewar and Fahey[21] have observed that the ionic addition of hydrogen bromide to acenaphthalene or 1-phenylpropene proceeds predominantly *cis*, the ratio of *cis* to *trans* product decreasing in going from nonpolar to polar solvents. The *trans* adduct was shown to be a primary product of ionic addition and was not produced by a secondary isomerization

(13) (a) C. A. Grob in "Theoretical Organic Chemistry" (papers presented to the Kekulé Symposium organized by The Chemical Society, London, Sept 1958), Butterworths Publications Ltd., London, 1959, p 114 ff; (b) C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955); C. A. Grob, *Experientia*, **13**, 126 (1957); (c) R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1952 (1957), and references cited therein; (d) D. H. Gustafson and W. F. Erman, *J. Org. Chem.*, **30**, 1665 (1965), and references cited therein.

(14) (a) D. H. R. Barton, *Experientia*, **6**, 316 (1950); (b) see also E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 219–234.

(15) N. C. Webb and M. R. Becker, *J. Chem. Soc, Sect. B*, 1317 (1967).

(16) This observation is in accord with previous reports that fully saturated bicyclo[3.3.1]nonane compounds exist in the twin-chair conformation.[17] It is noteworthy that introduction of an sp^2 carbon at the 1-carbon bridge (thereby removing a 1,4-hydrogen–hydrogen interaction in the boat conformation [*i.e.*, i *vs.* ii]) does not alter the conformation of the bicyclo[3.3.1]-nonane structure in the crystal form.



(17) (a) W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964); W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965), and references cited therein; (b) G. Eglinton, J. Martin, and W. Parker, *ibid.*, 1243 (1965).

(18) (a) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964); (b) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 47, 48, 136–138.

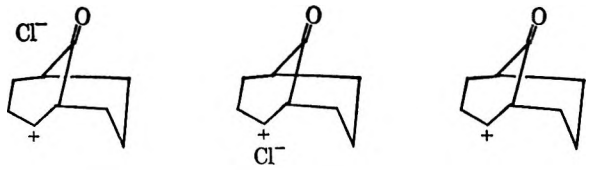
(19) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Ltd., London, 1959, p 116.

(20) It must be emphasized that these are only approximate couplings since the C-2–H and C-3–H resonances are strongly perturbed by mutual coupling and coupling with adjacent protons.[18b]

(21) (a) M. J. S. Dewar and R. C. Fahey, *J. Amer. Chem. Soc.*, **85**, 3645 (1963); (b) **85**, 2248 (1963); (c) **85**, 2245 (1963); (d) **84**, 2012 (1962).

of the initially produced *cis* isomer or by a radical addition. These results were inconsistent with a simple π-complex mechanism, previously proposed for hydrogen bromide additions, or a concerted process involving a four-centered cyclic transition state. The authors proposed instead a mechanism involving a classical carbonium ion formed in the rate-determining step as an ion pair with an acid-complexed halide ion. The ion pair either collapses to *cis* product or rearranges to a *trans* ion pair which then produces *trans*-addition product. Whether rearrangement from *cis* ion pair to *trans* ion pair occurs faster than collapse of *cis* ion pair to *cis* product depends upon the structure of the olefin involved and the polarity of the solvent system.[22,23]

In an analogous manner, then, the acid chloride **1** could interact with the olefin to produce the *exo*-chloro ion pair **10**. The chloride could be associated with hydrogen chloride (formed by partial decomposition of the acid chloride to the corresponding ketene), with solvent, or with aluminum chloride, when the latter catalyst is employed. The rate of rearrangement to *endo*-chloro ion pair **11** relative to collapse to **2** would be affected by the degree of association of chloride ion with the species mentioned above, the relative bulk of the associating species, and the relative stability of the carbonium ion.



10, *exo*-Cl **11**, *endo*-Cl **12**

The production of predominantly *endo* isomer in the presence of aluminum chloride and predominantly *exo* isomer in the absence of aluminum chloride is consistent with this mechanistic picture. Complex formation with aluminum chloride should lead to more rapid dissociation and rearrangement of ion pair **10**. In fact, dissociation in this instance could be concerted with attack of $AlCl_4^-$ of Cl^- from the *endo* side of the molecule.[23] Conversely, in the absence of aluminum chloride, ion pair **10** might be expected to collapse to *exo* isomer faster than dissociation or rearrangement to **11**.

Also consonant with the observed stereochemical course of addition, however, is the proposal that chloride ion adds from the least-hindered side of the completely dissociated ion **12**[24] in the absence of complexing agents to give *cis* product. Complex formation between the carbonyl function and aluminum chloride might sterically retard attack from the *exo* side of the molecule and lead to *endo* product. These and other influencing factors on the course of stereochemical addition to the present model make obvious the necessity for further studies on other systems in order to fully elaborate the mechanism of acyl halide additions to olefins.

Finally, the synthetic contribution of this work should be recognized. Of various preparations of bicyclo[3.3.1]nonane derivatives,[5,6,12,17b,c,25] the cyclization of the readily prepared acid chloride **1** represents one of the simplest laboratory approaches to these structures. It is the only method, in fact, which produces significant quantities of readily separated 2-*exo*-substituted isomers of this bicyclic system. The solvolysis of the latter derivative should give us a better insight into the chemistry of carbonium ion intermediates of type **12**.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary apparatus or on a micro hot stage and are corrected; boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 421 spectrophotometer or a Perkin-Elmer Model 137 infrared spectrophotometer as indicated. Nuclear magnetic resonance spectra were run on a Varian HA-100 spectrometer using tetramethylsilane as an internal reference. Chemical shifts are recorded as ppm on the τ scale, with coupling constants as hertz (Hz). Nuclear magnetic resonance data are recorded in the order: chemical shift, multiplicity where s is singlet, d doublet, t triplet, and m multiplet (coupling constant), integration (interpretation). Microanalyses were performed by T. Atanovich and associates of these laboratories and by Spang Microanalytical Laboratories, Ann Arbor, Mich. The monoglyme and diglyme solvents were freshly distilled from calcium hydride before use. Gas chromatography retention times are recorded relative to air.

Cyclooct-4-*cis*-ene-1-carboxylic Acid Chloride (1).—To 190.4 g (1.235 mol) of cyclooct-4-*cis*-ene-1-carboxylic acid[4b] was added dropwise with stirring 200 g (1.576 mol) of oxalyl chloride under a nitrogen atmosphere at such a rate that the temperature was maintained between 26 and 30°. After the addition was complete, the reaction mixture was stirred an additional 18 hr at room temperature. The excess oxalyl chloride was removed by evaporation at 40° (25 mm), and the residue was distilled under vacuum. Cyclooct-4-*cis*-ene-1-carboxylic acid chloride (1), 185.5 g (86%), was obtained as a colorless liquid: bp 92° (4.6 mm); infrared (Infracord), λ_{max}^{neat} 5.58 μ (C=O), 6.08, 14.2 μ (*cis*-olefin); nmr spectrum (10% in CCl_4), τ 4.38, m, 2 H (C-4 and C-5 protons), τ 7.25, m, 1 H (C-1 proton), τ 7.4–9.0, m, 10 H (C-2, C-3, C-6, C-7, C-8 protons).

Anal. Calcd for $C_9H_{13}OCl$: C, 62.6; H, 7.6; Cl, 20.5. Found: C, 62.9; H, 7.4; Cl, 19.3.

Cycloaddition Reaction of Acid Chloride (1). A. Absence of Catalyst.—A solution of 10.0 g (0.058 mol) of acid chloride **1** in 15 ml of ethylene dichloride, bp 83–84°, was heated at reflux for 72 hr. The warm reaction mixture was poured into 100 ml of warm water (40–50°) and stirred at this temperature for 1 hr. The mixture was cooled to 27° and extracted with three 35-ml portions of ether. The combined ether layers were washed with three 50-ml portions of water, dried, and solvent evaporated to yield 9.2 g of light brown liquid. The liquid was distilled in a modified Hickman still to afford 6.340 g of colorless liquid, bp 90–110° (0.1 mm). Gas chromatographic analysis on a 10 ft × 0.25 in. column packed with 20% ethylene glycol succinate polymer on 60–80 mesh Chromosorb W-HMDS at 200° with a flow of 60 cc of helium per min showed the presence of 2-*exo*-chlorobicyclo[3.3.1]nonan-9-one (**2**) (65%, relative retention time 28.9 min), 2-*endo*-chlorobicyclo[3.3.1]nonan-9-one (**3**) (24%, relative retention time 14.5 min), bicyclo[3.3.1]non-2-en-9-one (**4**) (7%, relative retention time 5.8 min). Samples

(22) For an analysis of *cis vs. trans* electrophilic additions to other olefin systems, see references cited in footnote 21, ref 15–18, 20, 21, 23; in W. F. Erman, *J. Org. Chem.*, **32**, 765 (1967), footnote 21; and in several articles by Cristol: S. J. Cristol, T. C. Morrill, and R. A. Sanchez, *ibid.*, **31**, 2719, 2726, 2733 (1966); S. J. Cristol and R. Caple, *ibid.*, **31**, 2741 (1966).

(23) The question arises as to whether part of the *endo* product is generated by attack of chloride ion on the π complex i (particularly in the presence of $AlCl_3$). Although this possibility cannot be overruled without further experimentation, the π complex i certainly cannot play an *important* role in product formation in the absence of added catalyst since the *cis*-addition product predominates under these conditions. Only *exo* product would be anticipated from an attack of a chloride ion species on the π complex i.

i

(24) In analogy, sodium borohydride reduction of bicyclo[3.3.1]nonan-2-one occurs predominantly from the *exo* side to give 2-*endo*-hydroxybicyclo[3.3.1]nonane.[3b]

(25) S. Brewis and P. R. Hughes, *Chem. Commun.*, 6 (1966).

of **2**, **3**, and **4** were collected by preparative glpc under the conditions described above, and their identities were established by nmr and infrared spectral comparisons with authentic specimens prepared as described under separate headings below.

When other solvents were employed, comparable results were obtained. The solvent, temperature, and yield of each product is listed in order for each run. The reaction period (72 hr) and work-up conditions were identical with those described above: (1) benzene, 80°; **2**, 34%; **3**, 13%; **4**, 4%; (2) monoglyme, 83°; **2**, 39%; **3**, 9%; **4**, 4%; methyl cyclooct-4-*cis*-ene-1-carboxylate, 9%; (3) 1,1,2-trichloroethane, 113°; **2**, 41%; **3**, 20%; **4**, 3%; (4) acetic acid, 118°; **2**, 27%; **3**, 15%; **4**, 7%; unidentified acetate, 25%.

B. In Diglyme Using Boron Trifluoride Etherate As Catalyst. Preparation of Bicyclo[3.3.1]non-2-en-9-one (4).—To a solution of 50.0 g (0.29 mol) of acid chloride **1** in 1 l. of anhydrous diglyme was added 50 ml of boron trifluoride etherate. This mixture was heated at 100° under a nitrogen atmosphere for a period of 72 hr. To the cooled solution (26–27°) was added dropwise 100 ml of water. The mixture was further diluted with 2 l. of water and stirred for 1 hr. The precipitated liquid was extracted with four 200-ml portions of ether. The combined ether extracts were washed with two 100-ml portions of water, dried over $MgSO_4$, and evaporated to yield 32.0 g of brown liquid. Gas chromatographic analysis on a 10 ft × 1/4 in. column packed with 20% GE-SF-96 silicon oil on 60–80 mesh Chromosorb W-HMDS at 200° with a flow of 60 cc of helium per min showed the presence of olefin **4** (65%) (relative retention time 3.3 min), methyl cyclooct-4-*cis*-ene-1-carboxylate (17%) (relative retention time 4.0 min, identified by comparison with an authentic sample[10]), chloro ketone **3** (5%) (relative retention time 5.7 min), chloro ketone **2** (7%) (relative retention time 7.0 min) and an unidentified compound (6%) (relative retention time 9.5 min). The liquid was dissolved in 200 ml of 10% methanolic potassium hydroxide solution, and this mixture was heated at reflux for 3 hr. The solution was diluted with 200 ml of water and extracted with three 100-ml portions of ether. The combined ethereal extracts were washed with three 50-ml portions of water, dried, and the ether removed under reduced pressure to afford 21.2 g (53%) of light yellow solid, mp 90–96°. Sublimation of this solid at 70° (25 mm) gave 10.0 g (25%) of **4** as colorless needles, mp 95–98°. The nmr and infrared spectral properties and glpc retention time of this material were identical with an authentic specimen of **4** prepared by the method of Foote and Woodward.[5] The 2,4-dinitrophenylhydrazone derivative, on recrystallization from ethanol–ethyl acetate, had mp 193–194° (lit.[5] mp 194.5–195.5°).

C. Using Aluminum Chloride As Catalyst. Preparation of 2-*endo*-Chlorobicyclo[3.3.1]nonan-9-one (3).—A mixture of 10.0 g (0.058 mol) of cyclooct-4-*cis*-ene-1-carboxylic acid chloride (**1**) and 0.050 g (0.0004 mol) of aluminum chloride in 30 ml of diglyme was heated under a nitrogen atmosphere at 100° for 16 hr. The mixture was cooled to 26–27° and 100 ml of water was added dropwise with stirring over a 10-min period. The mixture was stirred an additional 1 hr and was extracted with three 100-ml portions of ether. The ethereal extract was washed with three 50-ml portions of water, dried, and the ether evaporated to afford 8.502 g of dark brown liquid. The liquid was distilled in a modified Hickman still to yield 6.058 g of colorless liquid, bp 90–105° (0.1 mm). Gas chromatographic analysis on a 10 ft × 0.25 in. column packed with 20% Reoplex-400 on 60–80 mesh Chromosorb W-HMDS at 200° with a flow of 60 cc of helium per min showed the presence of **4** (30%, relative retention time 2.2 min), **2** (14%, relative retention time 8.0 min), **3** (33%, relative retention time 4.5 min). Samples of the olefinic ketone **4** and the *exo*-chloro ketone **2** were collected by preparative glpc, and their identity was established by nmr and infrared spectral comparisons with samples prepared under the respective headings. A sample of the *endo*-chloro ketone **3** was collected by preparative glpc as colorless needles: mp 65–66.5° (20% yield); infrared (Perkin-Elmer 421), ν (5% CS_2) 2985 cm^{-1} (abnormal C–H stretching), 1729 (strong), 1713 (weak) (C=O); nmr (10% CCl_4), τ 5.78, m (total band width 24 Hz), 1 H (C-2-*exo* proton). Irradiation of the C-1 proton indicated J (H-2, H-3-*exo*) = 4.9 Hz; J (H-2, H-3-*endo*) = 12.0 Hz.

Anal. Calcd for $C_9H_{13}OCl$: C, 62.6; H, 7.6; Cl, 20.5. Found: C, 62.7; H, 7.9; Cl, 19.8.

When monoglyme was employed as solvent under the same conditions, the yields of **2**, **3**, and **4** were 33, 14, and 30%, respectively.

Preparation of 2-*exo*-Chlorobicyclo[3.3.1]nonan-9-one (2).—A solution of 8.0 g of the crude product (before distillation) from cyclization of **1** as described in procedure A, above, and 10.0 g of potassium *t*-butoxide in 100 ml of wet *t*-butyl alcohol was stored at 26–27° for a period of 16 hr. The mixture was diluted with 100 ml of water and extracted with three 100-ml portions of petroleum ether (bp 41–45°). The combined petroleum ether extracts were washed with water (50 ml), 5% hydrochloric acid (50 ml), and three 100-ml portions of water and dried over magnesium sulfate. Removal of solvent under reduced pressure afforded 3.0 g of **2** (34% yield based on starting acid chloride **1**) as colorless needles, mp 64–67°. Recrystallization from acetone afforded **2** as colorless needles: mp 70–72°; infrared (Perkin-Elmer 421), ν (10% in CS_2), 2995 cm^{-1} (abnormal C–H stretching), 1732 (weak), 1728 (strong), 1707 (weak) (C=O); nmr (10% CCl_4), τ 5.46, m (total band width 10.5 Hz), 1 H (C-2-*endo* proton).

Anal. Calcd for $C_9H_{13}OCl$: C, 62.6; H, 7.6; Cl, 20.5. Found: C, 62.6; H, 7.6; Cl, 20.3.

Treatment of Bicyclo[3.3.1]non-2-en-9-one (4) with 10% Methanolic Sodium Hydroxide Solution.—A solution of 250 mg (0.0018 mol) of **4**, mp 95–98°, in 30 ml of 10% methanolic sodium hydroxide solution was heated at reflux under a nitrogen atmosphere for a period of 16 hr. The mixture was cooled to 26–27°, diluted with 50 ml of water, and extracted with three 25-ml portions of ether. The combined ethereal layers were washed with three 25-ml portions of water, dried, and the solvent evaporated to afford 187 mg (75%) of starting **4** as colorless prisms, mp 97–99°. The identity was further established by nmr and infrared spectral comparisons with an authentic specimen.[4] A mixture melting point with an authentic specimen (mp 95–98°) showed no depression (94–99°).

Treatment of 2-*exo*-Chlorobicyclo[3.3.1]nonan-9-one (2) with 10% Methanolic Sodium Hydroxide Solution.—A solution of 250 mg (0.0014 mol) of *exo*-chloro ketone **2**, mp 67–69°, in 30 ml of 10% methanolic sodium hydroxide solution was heated at reflux under a nitrogen atmosphere for a period of 16 hr. Work-up as above afforded 183 mg (95%) of keto olefin **4** as colorless prisms, mp 95–98°. The identity was confirmed by spectral comparisons and mixture melting point with an authentic specimen,[5] as above.

Treatment of 2-*endo*-Chlorobicyclo[3.3.1]nonan-9-one (3) with 10% Methanolic Sodium Hydroxide Solution.—A solution of 250 mg (0.0014 mol) of chloro ketone **3** in 30 ml of methanolic sodium hydroxide was heated as above. The cooled mixture was diluted with 50 ml of water and the neutral products extracted with three 25-ml portions of ether. The ethereal layers were combined, washed with three 25-ml portions of water, dried, and the solvent evaporated to afford 15 mg of light yellow liquid. The basic layer was cooled to 0–5° and acidified with concentrated hydrochloric acid. The resulting liquid was extracted with two 50-ml portions of ether. The ethereal solution was washed with three 25-ml portions of water and dried over magnesium sulfate. Evaporation of the ether afforded 203 mg (91%) of light yellow liquid: infrared (Infracord), λ 3–4 μ (carboxyl OH), 5.91 (carboxyl C=O). The liquid was dissolved in 25 ml of ether and treated with 50 ml of 2% ethereal diazomethane at 0° for 3 hr. The excess diazomethane was destroyed by addition of 15 ml of 10% hydrochloric acid; the ethereal layer was washed with 10 ml of 10% hydrochloric acid, two 20-ml portions of water, 25 ml of 10% sodium bicarbonate, and three 20-ml portions of water and dried. Evaporation of ether and short-path distillation afforded 166 mg of colorless liquid: bp 50–60° (0.5 mm); infrared (Infracord), λ 5.75, 8.1–8.6 μ (ester), 6.08, 13.35, 14.0 (*cis*-olefin). Gas chromatographic analysis on a 150-ft capillary column packed with polyphenyl ether and programmed from 100 to 180° with a heating rate of 5° per min with a helium flow of 20 cc per min showed the presence of methyl cyclooct-4-*cis*-ene-1-carboxylate (**6a**, 95%, relative retention time 14.62 min), methyl cyclooct-3-*cis*-ene-1-carboxylate (**7a**, 5%, relative retention time 14.26 min). The infrared and nmr spectra and the glpc retention times of each were identical with authentic samples[10] of the esters **6a** and **7a**.

Treatment of 2-*exo*-Chlorobicyclo[3.3.1]nonan-9-one (2) with Aluminum Chloride in Benzene.—A mixture of 1.00 g (5.8×10^{-3} mol) of **2**, mp 67.5–69°, and 0.50 g (3.8×10^{-3} mol) of aluminum chloride in 50 ml of benzene was heated at reflux under a nitrogen atmosphere for a period of 16 hr. The cooled mixture (26–27°) was poured into 200 ml of ice–water. The benzene layer was partitioned, washed with three 25-ml portions of

water, and dried and solvent removed under reduced pressure to afford 800 mg (80% recovery) of crystalline solid. Glpc analysis on a 10 ft × 0.25 in. column packed with 20% GE-SF-96 silicon oil on 60–80 mesh Chromosorb W-DMCS at 200° and helium flow of 65 cc/min indicated the presence of **2** (96%), trace quantities of **4**, and several unidentified peaks. No evidence for the *endo*-chloro epimer **3** was observed. A sample of **2** collected by preparative glpc showed mp 70–72°. A mixture melting point with an authentic specimen of **2**, mp 67.5–69°, showed no depression, mp 67.5–69.5°.

Treatment of 2 with Aluminum Chloride in Diglyme.—A mixture of 1.00 g (5.8×10^{-3} mol) of **2**, mp 67–69°, and 10 mg (7.5×10^{-5} mol) of aluminum chloride in 3 ml of diglyme was heated under a nitrogen atmosphere at 100° for 16 hr. After work-up as above there was isolated 840 mg (84% recovery) of **2** as colorless crystals, mp 69–71°; there was no depression of melting point on admixture with an authentic specimen of **2**.

Treatment of Olefin 4 with Aluminum Chloride in Diglyme.—A mixture of 1.47 g (1.08×10^{-2} mol) of **4** and 20 mg (1.5×10^{-4} mol) of aluminum chloride in 5 ml of diglyme was heated at 100° for 16 hr. After work-up as above there was isolated 1.37 g (93% recovery) of **4** as colorless crystals, mp 94–98°. A mixture melting point with the starting material **2**, mp 97–99°, showed no depression, mp 94–98°.

Treatment of 4 with Hydrogen Chloride–Aluminum Chloride in Diglyme.—A solution of 1.00 g (7.4×10^{-3} mol) of **4** and 20 mg (1.4×10^{-4} mol) of aluminum chloride in 5 ml of diglyme, saturated with gaseous hydrogen chloride, was heated at 100° for 6 hr. After work-up as above there was isolated 870 mg of soft crystals. Glpc analysis on a 10 ft × 1/8 in. column packed with 20% Reoplex on 60–80 mesh Chromosorb W-DMCS at 200° with a helium flow of 60 cc/min showed **2** (91%, relative retention time 4.3 min), the chloro ketone **3** (2%, relative retention time 10.0 min), four unidentified chloro ketones: relative retention times 11.3 min (2%), 11.7 (2%), 12.8 (1%), 13.0 (0.3%) and **2** (0.4%, relative retention time 18.0 min).

Registry No.—**1**, 15973-61-2; **2**, 16031-45-1; **3**, 16031-46-2; **4**, 4844-11-5; **6a**, 16031-48-4; **7a**, 15973-62-3.

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Iron Carbonyl Catalyzed Isomerization of Unsaturated Ethers and Esters. The Effect of Carbomethoxy and Methoxy Groups on Olefin Equilibria[1]

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Equilibrations of the double bonds in methyl *n*-alkenyl- and cyclohexenylcarboxylates and ethers have been studied. Iron pentacarbonyl in hydrocarbon solvents at reflux (125–150°) or with ultraviolet light at 20° was used to catalyze isomerization. Distribution of the double bonds to all possible positions is found with this catalyst system. For example, the equilibrium distribution of methyl octenoate isomers is 2-octenoate, 18%; 3-octenoate, 8%; 4-octenoate, 21%; 5-octenoate, 24%; 6-octenoate, 29%; and 7-octenoate, 1%. Equilibration of methyl pentenyl isomers gave the distribution 1-pentenyl, 86%; 2-pentenyl, 5%; 3-pentenyl, 8%; and 4-pentenyl, 1%. These data are rationalized on the basis of two main effects: (a) the inductive electron-withdrawal destablization effect of the carbomethoxy and methoxy groups and (b) the conjugative stabilization effects of these groups. The net effect of a carbomethoxy group on the stability of an α,β isomer is approximately that of an alkyl group. A methoxy group stabilizes an α,β isomer by a factor of 10 compared to an alkyl group. The relatively low percentages of β,γ isomers found in both series are explained by the inductive destabilization effect of the $-CH_2CO_2CH_3$ and $-CH_2OCH_3$ groups.

Several transition metal compounds have recently been used as extremely efficient isomerization agents of *n*-olefins.[2] For example, Asinger and coworkers[3] have described the double bond isomerization of 1-undecene to an equal distribution of internal isomers by iron pentacarbonyl catalyst at 50° for 1 hr in the presence of ultraviolet light. Other workers[4,5] have shown that the mixture of isomers from iron carbonyl catalyzed isomerizations closely parallels the theoretical thermodynamic equilibrium values. The use of iron carbonyls to catalyze the isomerization of unsaturated alcohols to aldehydes and ketones has been reported.[6,7] Enol alcohols formed in these isomerizations are irreversibly converted into their carbonyl forms, precluding a study of olefin equilibrium in those systems. We wished to use iron carbonyl catalysts for the isomerization of functionally substituted olefins under conditions of reversible equilibrium. By a comparison of the relative percentages of olefin isomers at equilibrium, the effect of the functional group on the relative stability of the various olefin isomers can be ascertained.

Almost four decades ago, Kon and Linstead and collaborators[8] investigated the effects of carbonyl and cyano groups on three carbon atom olefin equilibria as depicted in eq 1. Their results show that the carbonyl

$$\underset{1}{RCH_2CH_2CH{=}CHX} \overset{B^-}{\rightleftharpoons} \underset{2}{RCH_2CH{=}CHCH_2X} \qquad (1)$$

R = alkyl
X = CO_2R, CO_2H, CN, COR′

or cyano substituents favor isomer **1** over isomer **2** by a factor of 2–11:1. Under the basic isomerization conditions employed, migration of the double bond further down the chain in **2** is extremely slow due to the low acidity of the unactivated allylic hydrogen atoms compared to the hydrogen atoms adjacent to the substituent in **2**.

(1) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967, Abstracts, p O159.

(2) For up-to-date discussions on the mechanism of olefin isomerization by transition metal catalysts, see R. Cramer and R. V. Lindsey, Jr., *J. Amer. Chem. Soc.*, **88**, 3534 (1966), and M. Orchin, *Advan. Catal.*, **16**, 1 (1966).

(3) (a) F. Asinger, B. Fell, and K. Schrage, *Chem. Ber.*, **98**, 372 (1965); (b) *ibid.*, 381 (1965).

(4) M. D. Carr, V. V. Kane, and M. C. Whiting, *Proc. Chem. Soc.*, 408 (1964).

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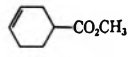
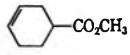
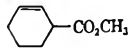
(6) G. F. Emerson and R. Pettit, *J. Amer. Chem. Soc.*, **84**, 4591 (1962).

(7) R. Damico and T. J. Logan, *J. Org. Chem.*, **32**, 2356 (1967).

(8) Recently discussed by D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, pp 201–202.

TABLE I

COMPOSITION OF EQUILIBRIUM MIXTURES FROM OLEFINIC ESTER ISOMERIZATIONS[a]

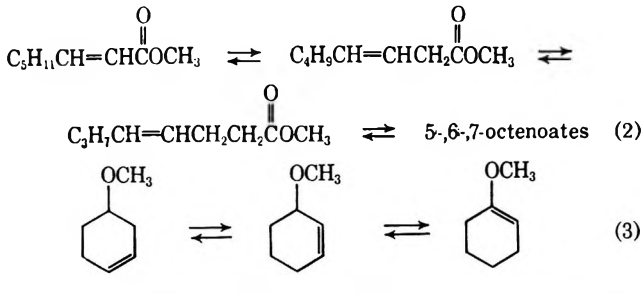
Entry[h]	Substrate	Time,[b] hr	Positional isomer, %[c] 1	2	3	4	5	6	7	Recovery, %	Purity,[d] %
1	$C_5H_{11}CH{=}CHCO_2CH_3$	24	...	18.1 (20.2)	8.1 (9.6)	20.4	23.6	28.5	1.5	92[e]	97
2	$CH_2{=}CH(CH_2)_5CO_2CH_3$	72	...	17.8 (16.5)	7.3 (8.2)	20.8	24.2	28.7	1.2	88[e]	97
3		72[f]	88.8 (87)	3.6 (~5)	7.6	...	...	...	...	95	98
4		48[g]	88.9	3.8	7.3	...	...	...	...	96	98
5		72	86.8	4.4	8.8	...	...	...	...	95	99

[a] Isomerization method A at 125° was used exclusively for these reactions. [b] The reaction time needed to reach equilibrium is reported. [c] Octenoate isomer percentages were determined by oxidative cleavage; cyclohexenyl isomer percentages were determined by quantitative gas chromatography. Values in parentheses for both series were determined by nmr analyses. [d] Per cent purity of samples was determined by gas chromatography. [e] Recovery percentages were calculated after distillation. [f] Addition of 30% excess $Fe(CO)_5$ and continued refluxing for 3 days after this time did not change the isomer percentages reported. [g] A temperature of 150° was used for this reaction. [h] Registry no.: 1, 2396-85-2; 2, 15766-90-2.

In an equilibrium system of the type shown in eq 1 the difference in stability between 1 and 2 is due to the difference in stabilizing effects of an X group and a $-CH_2X$ group; however, it is difficult to explain this by any one factor. The major problem is that while the α,β isomer is influenced by conjugative and inductive interactions with the functional group, the β,γ isomer is mainly affected by the inductive effect of the $-CH_2X$ moiety. Thus, a question of whether 1 is favored over 2 owing to conjugative stabilization of 2 becomes apparent. To examine this question we have isomerized olefinic ethers[9] and esters with iron pentacarbonyl catalyst to equilibrium mixtures of isomers where the double bonds are distributed to all possible positions. In such systems, the isomers in which the double bonds are located at least two carbon atoms from the functional groups are very similar to unsubstituted internal olefins. Comparison of the relative stability of these isomers with the isomers in which the double bonds are located next to, or one carbon atom removed from, the functional group gives an accurate evaluation of the effect of the functional group on the equilibria in question.

Results

Several acyclic and cyclic unsaturated esters and ethers have been prepared and isomerized with iron pentacarbonyl. Equilibria of the type shown in eq 2 and 3 have been studied.



Two methods of isomerization with iron pentacarbonyl were used. One method consists of refluxing the substrate in octane or nonane solvent at 125–150° with 10–20 mol % of iron pentacarbonyl for periods of 24–96 hr. The catalyst is added in increments of 5–10% during isomerization. We will refer to this isomerization procedure as method A. The alternative method employs iron carbonyl with ultraviolet irradiation, similar to the method developed by Asinger[2] for the isomerization of *n*-olefins. A 200-W high pressure mercury lamp at 20° with 3–5% iron carbonyl in pentane solvent gave complete isomerization within 0.25 to 8 hr with the compounds studied (method B). The results from the isomerization of unsaturated esters and ethers are given in Tables I and II. The effect of alkenyl chain length on the equilibrium mixtures of methyl alkenyl ethers is shown in Figure 1.

The time necessary to reach equilibrium was determined by gas chromatography and infrared spectral analysis of the reaction solutions. For example, gas chromatographic analysis of the isomerization reaction of methyl 2-octenoate (entry 1, Table I) showed four peaks on a 10-ft 20M Carbowax column at 125°. When the relative ratios of these four peaks reached constant values, the isomerization reaction was stopped. Similarly, the isomerization mixture from methyl 7-octenoate (entry 2, Table I) indicated four gas chromatography peaks which attained the same relative ratios as the peaks from the 2-octenoate isomer. Addition of excess iron pentacarbonyl and continued heating did not change the relative ratio of these peaks. Verification that an equilibrium distribution of double bonds had been reached was obtained by oxidative cleavage and nmr analysis of each isomerization mixture.

The isomerization of methyl 1- and 4-pentenyl ethers was followed by gas chromatography in a similar manner and by infrared spectral analyses. Relative intensities of the infrared peaks attributable to *trans* and *cis* α,β-unsaturated ethers[10] at 935 and 1250 cm^{-1}, respectively, compared to *trans* olefin absorption at 965 cm^{-1} were used to determine when equilibrium was established.

During isomerization the change (if any) in iron carbonyl infrared peaks was noted. Under the thermal method of isomerization the bands at 2000 and 2020 cm^{-1}, attributable[11] to $Fe(CO)_5$, did not shift nor did

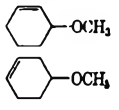
(9) A brief description of isomerization of unsaturated ethers with iron pentacarbonyl has previously been reported. No attempt was made to study the equilibrium distribution in this study. P. W. Jolly, F. G. A. Stone, and K. Mackenzie, *J. Chem. Soc.*, 6416 (1965).

(10) H. R. Warner and W. E. M. Lands, *J. Amer. Chem. Soc.*, **85**, 60 (1963).

(11) C. G. Barraclough, J. Lewis, and R. S. Nyholm, *J. Chem. Soc.*, 2582 (1961).

TABLE II

COMPOSITION OF EQUILIBRIUM MIXTURES FROM OLEFINIC ETHER ISOMERIZATIONS[a]

Entry[f]	Substrate	Time,[b] hr	Positional isomer, %[c] 1	2	3	4	Recovery, %	Purity,[d] %
1	$CH_3O(CH_2)_3CH=CH_2$	3	85[e]	5	9	1	90	97
2	$CH_3OCH=CH(CH_2)_2CH_3$	1	84[e]	6	9	1	91	98
3		6	93.5	2.9	3.6	...	93	98
4		5	(95) 95 (95)	2.0	3.0	...	96	98

[a] Isomerization method B was used exclusively in these studies. [b] The reaction time necessary to reach equilibrium is reported. [c] Pentenyl isomer percentages were determined by nmr analyses, cyclohexenyl isomers by gas chromatography on a 150 ft × 0.01 in. capillary column coated with polyphenyl ether. This column was purchased from the Perkin-Elmer Corporation. Values in parentheses determined by nmr analyses. [d] Purity percentages were determined by gas chromatography. [e] Approximately equal percentages of *cis* and *trans* 1-pentenyl ethers are present in these mixtures. Nmr and infrared spectral analyses were used to calculate the relative amounts of *cis* and *trans* enol ethers. [f] Registry no.: 1, 1191-31-7; 3, 2699-13-0; 4, 15766-93-5.

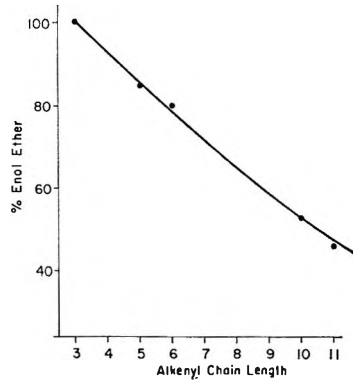


Figure 1.—Effect of alkenyl chain length on the percentages of enol ethers at equilibrium. Terminal alkenyl methyl ethers were isomerized by method B in this study.

new peaks appear. During irradiation, both shifting and new iron carbonyl peaks were discernible in the infrared spectra of the reaction solutions. Under the irradiation conditions, a typical spectrum has carbonyl peaks at 2085, 2055, 2025, and 2005 cm^{-1}. These spectra were independent of the particular ester or ether used.

After isomerization was complete the remaining iron carbonyl was destroyed by one of three methods. With esters, alcoholic ferric chloride oxidation of iron pentacarbonyl to ferrous chloride was effective in removing the last traces of catalyst. Alternatively, prolonged heating of the reaction solution converts essentially all iron carbonyls into elemental iron which is simply removed by filtration. Esters were then analyzed for double bond position, either directly or after distillation. This treatment did not affect the ratios of ester peaks in the gas chromatograms. The alcoholic ferric chloride method could not be used with ethers, due to the lability of enol ethers to acidic alcohol. If, however, irradiation of the ether reactions was continued long enough, insoluble metal carbonyls [$Fe_2(CO)_9$, etc.] were formed and separated by filtration. These isolation methods gave recoveries of 88–95% of esters and ethers which were shown to have purities of greater than 95% by various analyses (Tables I and II).

Evidence that a true equilibrium was reached in each case rests mainly upon the fact that at least two positional isomers were isomerized to the same equilibrium mixture for each type of compound studied. In most instances the two extreme positional isomers (*e.g.*, entries 1 and 2, Table I) were isomerized.

Analyses of the positional isomers was accomplished by oxidative cleavage, quantitative nmr, and gas chromatography analyses. Double bond isomers of esters were cleaved with permanganate–periodate; the resulting acids and acid esters were converted to their methyl esters, which were quantitatively analyzed by gas chromatography.[12] When possible, the percentages of α,β and β,γ isomers were calculated from the nmr spectra of the isomerized reaction mixtures. Olefinic and allylic peaks of the spectra were integrated to obtain these percentages. Good agreement with both oxidative cleavage and gas chromatography analyses was found and is reported in Tables I and II. Quantitative gas chromatography analysis was used when authentic samples of each positional isomer were available and when each isomer was separable. This was only possible in the cyclic series studied.

Discussion

A prime question in this study is the role of the iron carbonyl reagent; *i.e.*, whether it is solely a catalyst for isomerization or is involved in the formation of stable olefin–iron carbonyl complexes. We made several observations that indicate *stable* complexes are not formed under our isomerization conditions. First, careful examination of the infrared spectra of the reaction solutions during the thermal isomerization reactions showed no change occurring in the carbonyl peaks of $Fe(CO)_5$ at 2000 and 2020 cm^{-1}. If a stable olefin–iron carbonyl complex is formed during reaction, a separation of these peaks would be expected.[13] During isomerization method B the carbonyl peaks do shift and new bands are observed, but a similar phenomenon is found when $Fe(CO)_5$ is irradiated alone. This is due to the formation of other iron carbonyl species, such as

(12) This method has been reported by D. F. Kuemmel of these laboratories [*Anal. Chem.*, **36**, 426 (1964)].

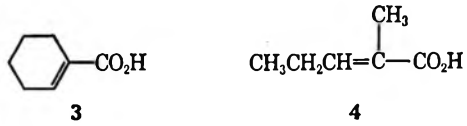
(13) A correlation between the electronic structure of the ligand and the carbonyl stretching frequencies in diene–iron tricarbonyl complexes has been discussed by R. Pettit and G. F. Emerson [*Advan. Organometal. Chem.*, **1**, 11 (1964)].

$Fe_2(CO)_9$ and $Fe_3(CO)_{12}$.[14a] Therefore, the fact that new bands are found cannot be taken as evidence that an iron carbon–olefin complex was formed. Second, the small amount (3–5%) of iron carbonyl necessary to establish equilibrium throughout an olefin molecule with isomerization method B argues against a specific olefin–iron carbonyl species being stable under the isomerization conditions. Third, the addition of amounts up to 30% of iron pentacarbonyl to mixtures which had attained equilibrium did not affect the relative isomer percentages or the high recovery (88–98%) of products with purities of greater than 95%. The latter observation is strong evidence against stable olefin complex formation.[14b]

The ability of $Fe(CO)_5$ to promote isomerization effectively under neutral condition is invaluable. Under the basic conditions of Kon and Linstead,[8] Michael addition of solvent to the α,β isomers was found. Other problems associated with basic catalysis include elimination and cleavage. Thus, Kesslin and Orlando[15] found that treatment of butenyl ethers with potassium *t*-butoxide gives exclusive elimination and no isomerization (eq 4). It is apparent, then, that a real need existed for an isomerization reagent of the type described in this study.

$$ROCH_2CH{=}CHCH_3 + t\text{-BuOK} \longrightarrow CH_2{=}CH{-}CH{=}CH_2 + ROK + t\text{-BuOH} \quad (4)$$

Our studies were concentrated on *n*-alkenyl and cyclohexenyl esters and ethers. The six-membered unsaturated ring system was chosen because this system appears to parallel closely its acyclic analog in isomerization studies.[16] Thus, Boorman and Linstead[17] have reported that 4% of the cyclic α,β isomer **3** was isomerized to the β,γ form, while 10% of its acyclic analog **4** was converted into the unconjugated isomer.



3 **4**

Turning our attention now to the effect of the substituent on the relative double bond stabilities, we wish to discuss two main factors, the resonance and inductive effects of the substituent groups.[18] Conjugative interactions, whether the substituent group is electron releasing (+R) or electron withdrawing (−R), are stabilizing factors. Thus, ether,[19a,b] amine,[19c] and sulfide[19d] substituents (+R groups) strongly favor the vinyl over the propenyl forms in the equilibria of three carbon atom systems, as do the isomerization reactions shown in eq 1 which have −R substituent groups. The role of −I and +I groups on olefin equilibria is less definitive. Electron releasing alkyl groups, especially unbranched groups, have been found to stabilize a double bond isomer when attached to the ethylenic carbon atom.[20] An interesting study[21a] of the effect of electron-withdrawing groups on the equilibria of sulfur-substituted, three carbon atom systems shows an increase in β,γ isomers with increasing −I effect of the groups $-SCH_3$, $-SOCH_3$, and $-SO_2CH_3$. This increase has been rationalized on the basis that an inductive withdrawal of electrons destabilizes the α,β double bonds in these systems.[21b] In our study the $-CO_2R$ group is reported[22] to have a −R and a −I effect, while the $-OCH_3$ group has a +R and −I effect. We have found that the average of equilibrium values from iron carbonyl catalyzed isomerization of methyl octenoate isomers is 18% 2-(α,β), 8% 3-(β,γ), 21% 4-, 24% 5-, 29% 6-, and 1% 7- (terminal) octenoates (entries 1 and 2, Table I). There are several important points to note concerning these isomerization results. The conclusion reached from the base-catalyzed isomerization of

(14) (a) $Fe_2(CO)_9$ is reported [R. K. Sheline and K. S. Pitzer, *J. Amer. Chem. Soc.*, **72**, 1107 (1950)] to have major infrared peaks at 2034 and 2080 cm^{-1} while $Fe_3(CO)_{12}$ has major absorptions at 2043, 2020, and 1997 cm^{-1} [F. A. Cotton and G. Wilkinson, *ibid.*, **79**, 752 (1957)]. Indeed, the recommended preparative method for $Fe_2(CO)_9$ is by irradiation of $Fe(CO)_5$ [R. B. King in "Organometallic Syntheses, Vol. I, Transition-Metal Compounds," J. J. Eisch and R. B. King, Ed., Academic Press Inc., New York, N. Y., 1965, p 93]; (b) a referee has suggested that iron carbonyl complexes with an oxygen atom of the ester or ether and the double bond of the α,β or β,γ isomer and that elimination of hydroiron carbonyl from these complexes controls the relative percentages of α,β and β,γ isomers. This explanation is unacceptable to us for several reasons. If the rate of formation of complexes and elimination of metal hydrides controlled the "equilibria" of α,β and β,γ isomers we would expect changes in relative percentages of these isomers with the addition of different amounts of iron pentacarbonyl and in prolonged reaction times. Neither one of these reaction changes affected the equilibrium values (note entry 3, Table I). A most convincing argument against the referee's suggestion is the observation that all equilibria were established by starting from at least two different positional isomers. It was further established that a stable intermediate is not formed under our isomerization conditions. Therefore, the equilibrium results reported here are the thermodynamic values.

(15) G. Kesslin and C. M. Orlando, Jr., *J. Org. Chem.*, **31**, 2682 (1966).

(16) It is important to choose a ring in which conformational effects are minimal. A study of equilibria between cycloalk-2- and -3-enones shows that for a six-membered ring the equilibrium composition is 99% Δ^2 and 1% Δ^3, while the nine-membered ring is >99.7% Δ^3 and <0.3% Δ^2 [N. Heap and G. H. Whitham, *J. Chem. Soc., Sect. B*, 164 (1966)].

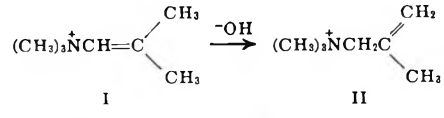
(17) E. J. Boorman and R. P. Linstead, *ibid.*, **258**, 1935.

(18) Other factors that can be considered are steric, solvation, and field effects and the possibility that differences in optical and geometrical isomers may influence the relative stability of positional isomers. Although an investigation of these effects was not undertaken, we do not believe that they are major contributing factors for the following reasons. In molecules of comparable size, such as those under investigation, we would expect small differences in steric factors between difficult positional isomers. Thus, equilibration of *n*-undecene isomers[3] yields the same percentage of 2, 3, 4, and 5 isomers despite the expected differences in steric effects. In our systems conformational effects may be important for double bonds isomers in close proximity to the functional groups, such as the α,β isomers. All reactions were conducted in hydrocarbon solvents in which solvation is unimportant. Comparison of the relative stability of cyclic isomers to acyclic isomers is clouded by the fact that β,γ and γ,δ cyclic isomers have *dl* pairs which contribute an entropy of mixing term (1.38 cal/deg mol) to the equilibrium in question. In addition, each cyclic isomer exists in one geometrical configuration while the acyclic isomer exists in two. Finally, no attempt has been made to distinguish between field effects and σ inductive effects. However, it should be noted that the relative ratios of β,γ and γ,δ isomers in both cyclic and acyclic esters are essentially constant despite the differences in steric and field effects and optical and geometrical isomers of these compounds. Assuming all of these effects are not fortuitously balanced, we can reason that they are not major factors which influence the relative stability of the β,γ and γ,δ isomers.

(19) (a) T. J. Prosser, *J. Amer. Chem. Soc.*, **83**, 1701 (1961); (b) C. C. Price and W. H. Snyder, *ibid.*, **83**, 1773 (1961); (c) C. C. Price and W. H. Snyder, *Tetrahedron Lett.*, **2**, 69 (1962); (d) D. S. Tarbell and W. E. Lovett, *J. Amer. Chem. Soc.*, **78**, 2259 (1956).

(20) For example, see A. Schriesheim and C. A. Rowe, Jr., *ibid.*, **84**, 3160 (1962), for the equilibrium compositions of 2-methylpentenes.

(21) (a) D. E. O'Connor and W. I. Lyness, *ibid.*, **86**, 3840 (1964); (b) equilibrium constants between I and II at 100 and 161° are 58.1 and 41.8, respectively, with II favored. The inductive electron-withdrawal destabilization of I can be used to explain these results. M. Saunders and E. H. Gold,



I II

ibid., **88**, 3376 (1966).

(22) Taft reports the following values of $\sigma_R = -0.50$ and $\sigma_I = +0.23$ for the $-OCH_3$ group, and $\sigma_R = +0.20$ and $\sigma_I = +0.32$ for $-CO_2R$ group. R. W. Taft, Jr. in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p 595.

methyl 2- and 3-hexenoates[23] was that the 2 isomer is favored relative to the 3 isomer at equilibrium. Our results, in agreement with this conclusion, indicate a ratio of 2.5:1 of α,β to β,γ octenoate isomers when complete distribution of double bond isomers is found. These results indicate that the relative stability of α,β and β,γ olefinic ester isomers is independent of these two isomerization methods. Surprisingly enough, the α,β isomer is *not* the favored isomer when compared to the other internal isomers. The average olefin per cent of the 4, 5, and 6 octenoate isomers (entries 1 and 2, Table I) is ~25%, slightly higher than the 18% observed for the α,β isomer. Of interest, also, is the small amount of β,γ isomer compared to α,β or to other internal isomers at equilibrium. To explain these data we propose that the carbomethoxy group influences the position of equilibrium by two main factors, conjugative stabilization and inductive electron-withdrawal destabilization effects. These two effects counterbalance one another when the double bond is in the 2 position so that the net result is that the α,β isomer is comparable in stability to the internal isomers not grossly influenced by the $-CO_2CH_3$ group. Inductive effects also appear quite important in influencing the relative stability of the other isomers. Thus, the 4, 5, and 6 isomers are each more stable than the β,γ isomer by a factor of 3 (~25:8). This observation can be rationalized by assuming that the −I destabilization effect is transmitted through one methylene unit to the β,γ isomer, while there is little effect of this group on the 4, 5, and 6 isomers.[24] It is evident from these results that a $-CH_2CO_2CH_3$ group is not equivalent to an alkyl group. Finally, the ratio of α,β to β,γ isomers can be explained by the inductive destabilization effect of the $-CH_2CO_2CH_3$ group on the β,γ isomer relative to the net stabilizing influence of the $-CO_2CH_3$ on the α,β isomer.

To test these proposals further we examined the isomerization of methyl cyclohexenyl carboxylate isomers (entries 3, 4, and 5, Table I). In this system the 1 isomer is favored over both the 2 and 3 isomers at equilibrium due to the additional stabilization of a $-CH_2$ unit at the α-carbon atom. Again, the γ,δ (3) isomer is favored over the β,γ (2) isomer. Since these two isomers have comparable alkyl substitution, the difference in stability can be attributed to the destabilization effect of the $>CHCO_2CH_3$ group on the 2 isomer.

The equilibrium isomer distributions of olefinic ethers demonstrate relative resonance and inductive effects. Conjugative stabilization of the $-OCH_3$ group is very important in these systems because a preponderance of the α,β isomer is formed in each case (Table II and Figure 1). In the acyclic compounds the equilibrium amount of enol ether varied between 46 and 100% depending on chain length, while 95% enol ether is formed during isomerization of the cyclohexenyl ethers. Examination of the relative amounts of 2 and 3 isomers from the isomerization of *n*-pentenyl and cyclohexenyl isomers (Table II) indicates that the inductive destabilization of the $>CHOCH_3$ group is important. The ratio of 3 isomer to 2 isomer is 1.5 to 1 in both series of compounds. Although the percentages of 3 and 2 cyclohexenyl isomers are small (3–3.6:2–2.9) it is significant that, starting with the 2 isomer (entry 3, Table II), more 3 than 2 was present when the equilibrium was reached.

Figure 1 shows the effect of alkenyl chain length on the per cent of α,β (enol) isomer at equilibrium. An increase in percentage of internal isomers and a decrease in α,β isomer with increasing number of possible internal isomers is evident from the graph. A ratio of enol ether to each internal ether (excluding β,γ) of ~10:1 can be obtained from these data and from the pentenyl ethers' equilibrium values. Therefore, replacement of an alkyl group with a methoxy group at a vinyl carbon atom increases the stability of this isomer by 1.5 kcal.[25]

Qualitatively, the inductive and resonance effects of the carbomethoxy and methoxy groups on olefin stability, as determined from this work, can be summarized. A carbomethoxy group influences the stability of an α,β isomer by opposing conjugative stabilization and inductive destabilization; the net effect of the $-CO_2CH_3$ unit is comparable to the inductive stabilization of an alkyl group. A $-CH_2CO_2CH_3$ group inductively destabilizes an olefin isomer by a factor of ~3 compared to an alkyl group. A methoxy group stabilizes an α,β isomer by a factor of 10, while a $-CH_2OCH_3$ destabilizes a β,γ isomer by ~1.5:1 compared to an alkyl group.[26]

Experimental Section[27]

Methyl 2-Octenoate.—This compound was prepared by methanol–sulfuric acid esterification of 2-octenoic acid (Aldrich Chemical Co.). After the normal work-up, distillation at 42–44° (1.4 mm) afforded the product in 98% purity by gas chromatography analysis. Oxidative cleavage analysis[12] of the double bond positions of this product showed that 89% was in the α,β form and 11% was in the β,γ form.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 68.9; H, 10.2.

An nmr spectrum has peaks centered at τ 3.3 (1 H, β vinyl proton), 4.4 (1 H, α vinyl proton), 6.4 (3 H, $—CO_2CH_3$), 7.9 (2 H allylic CH_2), 8.7 (8 H, alkyl CH_2), and 9.1 (3 H, alkyl CH_3). In addition, a small peak at τ 7.15, characteristic of the allyl protons adjacent to the carbomethoxy group in the β,γ isomer, was discernible.

Methyl 7-Octenoate.—A solution of 20.0 g (0.089 mol) of 8-bromooctanoic acid (Sapon Laboratories, Oceanside, N. Y.) and 32 g (0.29 mol, 50% excess) of potassium *t*-butoxide in 250 ml of *t*-butyl alcohol was refluxed for 3 hr. The mixture was

(23) G. A. R. Kon, R. P. Linstead, and G. W. G. Maclennan, *J. Chem. Soc.*, 2452, 2454 (1932).

(24) The distribution of the 4, 5, and 6 isomers indicates that a progressive diminishing of the $-CO_2CH_3$ inductive effect is in evidence. Although we favor this explanation, other factors, such as the change in the alkyl substituent, may cause this isomer distribution.

(25) Calculated from $\Delta F = -RT \ln K$. A value of 5.75 kcal conjugative stability (ca. 2.25 kcal relative to methyl) has been assigned to the methoxy group (see footnote 27 in C. D. Broaddus, *J. Amer. Chem. Soc.*, **87**, 3706 (1965)).

(26) These generalizations agree well with the reported σ_I and σ_R effects of these groups (*cf.* ref 22). They are also consistent with the σ_I reported values [M. Charton, *J. Org. Chem.*, **29**, 1222 (1964)] of the $-CH_2CO_2CH_3$ and $-CH_2OCH_3$ groups which are +0.17 and +0.07, respectively. Using these values we are tempted to make more quantitative comparisons of our results with these reported σ values. However, the recent literature describes the influence of substrate [M. Charton, *J. Org. Chem.*, **30**, 557 (1965)], solvent [R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709 (1963)], and other factors on both σ_R and σ_I values which may make such comparisons invalid.

(27) Boiling points are uncorrected. Infrared spectra were obtained on hydrocarbon solutions in a 0.015-mm cell with a Perkin-Elmer Infracord or a Model 21 spectrophotometer. Gas chromatographic separations were made on a 10 ft × 0.25 in. column packed with 20% Carbowax 20M on 60–80 mesh, acid-washed Chromosorb W, unless otherwise indicated. Nuclear magnetic resonance spectra were determined in carbon tetrachloride or deuterated chloroform solutions with a Varian Model HA-100 or A-60 spectrophotometer using tetramethylsilane as an internal standard.

cooled, acidified with sulfuric acid, diluted with water, and extracted with ether. The ether layer was evaporated under reduced pressure and the residue acid esterified with a solution of 2 ml of sulfuric acid and 35 ml of methanol. Distillation at 43–45° (0.45 mm) afforded 7.3 g (43%) of product which was 98% of one component by gas chromatography analysis; the nmr spectrum showed peaks at τ 4.3 (1 H, =CH—), 5.1 (2 H, $=CH_2$), 6.4 (3 H, $—CO_2CH_3$), 7.8 (2 H, $—CH_2CO_2—$), 8.2–8.7 (8 H, allylic CH_2 and $C—CH_2$), and 9.1 (3 H, $C—CH_3$).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.0; H, 10.2.

Methyl 1-Cyclohexene-1-carboxylate.—The method of Bailey and Baylouny[28] was used to prepare the ester in 57% yield: bp 47–50° (2 mm) (lit.[28] bp 86° (15 mm)); nmr spectrum, τ 3.2 (1 H, =CH—), 6.5 (3 H, $—CO_2CH_3$), 7.9 (4 H, allylic CH_2), and 8.5 (4 H, $C—CH_2$).

Methyl 2-Cyclohexene-1-carboxylate.—Metalation[29] of cyclohexene with *n*-butylsodium followed by carbonation and diazomethane esterification afforded the ester: bp 65–67° (7.5–8.0 mm) (lit.[29] bp 78–80° (20 mm)); nmr spectrum, τ 4.3 (2 H, CH=CH), 6.4 (3 H, $—CO_2CH_3$), 7.0 (1 H, C=C—CH—CO_2—), and 7.9–8.6 (6 H, allylic CH_2 and $C—CH_2$).

Methyl 3-Cyclohexene-1-carboxylate.—A stirred mixture of 22 g (0.2 mol) of 3-cyclohexene-1-carboxaldehyde (Columbia Organic Chemicals Co., Inc.) and 57 g (0.25 mol) of silver oxide[30] was heated at 50° for 2 hr and then maintained at room temperature for 12 hr. The mixture was acidified with concentrated hydrochloric acid, filtered to remove silver chloride, extracted with ether, and the ether layer evaporated to yield unpurified 2-cyclohexene-1-carboxylic acid. The acid was esterified with methanol–sulfuric acid and, after work-up, distilled at 48–49° (4.5 mm) (lit.[28] bp 80–82° (23 mm)). A total of 14 g (50%) of ester was recovered; the nmr spectrum gave signals at τ 4.4 (2 H, CH=CH), 6.4 (3 H, $—CO_2CH_3$), 7.55 (1 H, —CH—CO_2—), and 7.7–8.3 (6 H, allylic CH_2 and $C—CH_2$).

***n*-Hexyl allyl ether** was purchased from Peninsular Chem-Research Inc., Gainesville, Fla.

Methyl 1-Decenyl Ether.—Using the procedure of Warner and Lands[31] for the preparation of a similar compound, the alkenyl ether was prepared from decanal, methanol, and hydrogen chloride to produce methyl 1-chlorodecyl ether followed by elimination of hydrogen chloride with dimethylaniline. The product mixture was distilled at 45–55° (0.45 mm) to yield a mixture of dimethylaniline and methyl 1-decenyl ether. Final purification of the ether was accomplished by column chromatography on neutral alumina (Alupharm Chemicals, New Orleans, La., activity grade 2) using pentane as an eluent.[31] A gas chromatogram of the product showed 50% *cis*-, 50% *trans*-decenyl ethers; the nmr spectrum[32] gave signals at 3.8 and 4.3 (1 H, α-vinyl H of *trans* and *cis* isomers), 5.55 and 5.8 (1 H, β-vinyl H of *trans* and *cis* isomers), 6.55 and 6.80 (3 H, $—OCH_3$ of *cis* and *trans* isomers), 8.15 (2 H, allylic CH_2), 8.4–8.8 (12 H, $C—CH_2$), and 9.1 (3 H, $C—CH_3$).

Methyl 1-Pentenyl Ether.—Methyl 1-chloropentyl ether was prepared from pentanal, methanol, and hydrogen chloride according to the procedure of Warner and Lands.[31] The chloro ether was dehydrochlorinated by reaction with *sym*-collidine. Removal of *sym*-collidine hydrochloride by filtration, followed by distillation of the ether at 99–114° (760 mm), afforded the product which was purified by column chromatography on alumina using pentane as an eluent. A gas chromatogram showed the product was approximately 90% pure and consisted of 52% *cis* and 42% *trans*-methyl 1-pentenyl ether. The product contained pentanal (~8%) as the major impurity. An nmr spectrum was in accord with the structure.

Methyl 4-Pentenyl Ether.—A mixture of 4.8 g (0.2 mol) of sodium hydride and 20.0 g (0.2 mol) of 4-penten-1-ol (Chemical Samples Co., Columbus, Ohio) in 30 ml of hexane diluent was stirred at reflux under an argon atmosphere for 3 hr. After the mixture was cooled, 37 g (0.26 mol, 30% excess) of methyl iodide was added dropwise (exothermic reaction) over 25 min and then heated to reflux for 2 hr, cooled, poured into water, and extracted with ether. The separated ether layer was dried with 3-Å molecular sieves and distilled at 41–42° (35 mm) to yield 12.4 g (54%) of methyl 4-pentenyl ether which had a gc purity of 98%; the nmr spectrum showed peaks at τ 4.3 (1 H, =CH—), 5.1 (2 H, $H_2C=$), 6.7–6.9 (5 H, $CH_2—O—$ and $—O—CH_3$), 7.95 (2 H, allylic CH_2), and 8.4 (2 H, $C—CH_2$).

Methyl 5-hexenyl, 9-decenyl, and 10-undecenyl ethers were prepared in essentially the same manner as the 4-pentenyl ether. Gc purities were in each case greater than 98%. Nmr spectra were in accord with the indicated structures.

Methyl 2-Butenyl Ether.—This compound was prepared to determine the nmr position of an allylic methylene group adjacent to a methoxy function in an *n*-alkenyl ether. Preparation in the normal manner afforded a product of bp 78–78.5° (760 mm) which had a gc purity of ~99%; the nmr spectrum showed peaks at τ 4.4 (2 H, CH=CH), 6.2 (2 H, $—O—CH_2—C=C$), 6.7 (3 H, $—OCH_3$), and 8.3 (3 H, $=C—CH_3$).

1-Cyclohexen-1-yl methyl ether was prepared in 73% yield and 95% gc purity by acid-catalyzed elimination of methanol from cyclohexanone dimethyl ketal using the method described[33] for the preparation of 1-cyclohexen-1-yl ethyl ether. The enol ether distilled at 39–42° (15 mm); the nmr spectrum gave signals at τ 5.7 (1 H, vinyl H), 6.65 (3 H, $—OCH_3$), 8.05 (4 H, allylic CH_2), and 8.5 (4 H, $C—CH_2$).

2-Cyclohexen-1-yl Methyl Ether.—Using the procedure described for the preparation of methyl 4-pentenyl ether, this compound was prepared in 60% yield: bp 129–139° (760 mm); gc purity of 91% with a major impurity of 5% methyl cyclohexyl ether; the nmr spectrum gave signals at τ 4.32 (2 H, vinyl H), 6.4 (1 H, =C—CH—O—), 6.75 (3 H, OCH_3), 8.05 (2 H, allylic CH_2), and 8.4 (4 H, $C—CH_2$).

3-Cyclohexen-1-yl Methyl Ether.—Prepared from 3-cyclohexen-1-ol (Columbia Organic Chemicals Co., Inc.,) by the sodium hydride–methyl iodide method, this compound was distilled at 37–43° (18 mm) and shown to have a gc purity of only 71%. The mixture contained 24% of methyl cyclohexyl ether that was formed due to the starting alcohol containing 30% cyclohexanol impurity. Distillation of the alcohol did not separate cyclohexanol from 3-cyclohexen-1-ol. This impurity did not interfere with gc or nmr analyses of isomerized 3-cyclohexen-1-yl methyl ether. A gc collected sample of the ether had the following nmr spectrum: τ 4.5 (2 H, vinyl H), 6.6–6.75 and —O—CH—, (4 H, $—OCH_3$), and 7.8–8.7 (6 H, allylic CH_2 and $C—CH_2$).

Thermally Induced Iron Carbonyl Catalyzed Isomerizations of Alkenyl Esters.—These isomerization reactions were all conducted in a similar manner. The isomerization of methyl 2-octenoate (entry 1, Table I) is given as an example. A solution of 5 g (0.032 mol) of methyl 2-octenoate and 0.32 g (0.22 ml, 0.0016 mol, 5 mol %) of iron pentacarbonyl in 30 ml of octane was refluxed (~125°) under argon in a three-necked, 50-ml Bantamware (Kontes Glass Co., Vineland, N. J.) flask equipped with a rubber septum in one side arm. The reaction mixture turned dark within minutes after it reached 125° and black deposits of metallic iron were soon noted. Samples (1 ml) were withdrawn at 2, 5, 17, and 22 hr reaction times by the use of a hypodermic needle through the rubber septum. Infrared spectra of these samples were examined for peaks in the regions of iron carbonyl (1950–2050 cm), ester carbonyl (1720–1740 cm^{-1}), and vinyl CH deformation (890–1000 cm^{-1}) frequencies. During the course of the reaction no changes in the iron pentacarbonyl peaks (2000, 2020 cm^{-1}) were noted; the conjugated carbonyl peak (1740 cm^{-1}) decreased and a *trans* olefin peak[34] at 965 cm^{-1} became visible. After 17 hr of refluxing, the carbonyl and olefin peaks did not change in position or intensity. The iron pentacarbonyl peaks diminished noticeably in intensity during the 17 hr of reflux, and additional (10%) catalyst was added. Refluxing for 5 hr more did not change the infrared peaks. The samples were also analyzed by gas chromatography. Four peaks were separable on the gas chromatograph. After 22 hr

(28) W. J. Bailey and R. A. Baylouny, *J. Amer. Chem. Soc.*, **81**, 2126 (1959).

(29) Using the procedure of A. A. Morton and R. A. Finnegan, *J. Polymer Sci.*, **38**, 19 (1959). We thank Dr. D. Muck of these laboratories for providing us with a sample of 2-cyclohexene-1-carboxylic acid.

(30) Prepared by the method of E. Campaigne and W. M. LeSuer in "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, pp 919–921.

(31) H. R. Warner and W. E. M. Lands, *J. Amer. Chem. Soc.*, **85**, 60 (1963).

(32) The nmr spectra of alkenyl ethers have been analyzed by Warner and Lands,[31] T. J. Prosser [*ibid.*, **83**, 1701 (1961)], and C. D. Broaddus [*ibid.*, **87**, 3706 (1965)].

(33) A. Johannissian and E. Akunian, *Bull. Univ. État R.S.S. Arménie, No. 5*, 235, 245 (1930); *Chem. Abstr.*, **25**, 921, 922 (1931).

(34) K. Nakanishi, "Infrared Absorption Spectroscopy—Practical," Holden-Day, Inc., San Francisco, Calif., 1962.

the ratios were 3.84:3.00:1.00:1.22. The reaction mixture was cooled, filtered to remove metallic iron, and treated with 2.9 g (0.0182 mol) of ferric chloride in 20 ml of 95% ethanol. Gas evolution (CO) was noticed. This mixture was stirred for 2 hr, poured into salt water, and extracted with pentane. Distillation of the pentane extract, with tridecane added as a chaser solvent, yielded a fraction of bp 71–85° (18–20 mm) which contained octane, ester isomers, and tridecane. This mixture weighed 5.1 g, of which 4.1 g (92% recovery after correction for aliquot samples) was ester isomers as determined by quantitative gc. The ratio of gc peaks remained constant before and after ferric chloride treatment and distillation. An nmr spectrum showed peaks at 3.2 (β-vinyl H, 2 isomer), 4.35 (α-vinyl H, 2 isomer), 4.7 (vinyl H, internal isomers), 6.45 ($-CO_2CH_3$), 7.15 ($C{=}C-CH_2-CO_2-$), and other normal peaks of olefin ester internal isomers. Integration of the aforementioned peaks showed 20.2% of the 2 isomer and 9.6% of the 3 isomer. The mixture was analyzed by oxidative cleavage (Table I) to obtain the per cent of other internal isomers and to substantiate the nmr result.

An alternative in the work-up involved leaving out the ferric chloride treatment and destroying most of the $Fe(CO)_5$ catalyst by heating. In these cases the product was analyzed directly after filtration to remove metallic iron. Analyses of isomerized mixtures by gas chromatography were checked by preparing known molar concentration solutions of standards. For example, a prepared mixture of methyl cyclohexene carboxylate isomers containing 43.8% of the 1, 22.7% of the 2, and 34.5% of the 3 isomer was shown by gas chromatography to have 46.2% of 1-, 21.3% of 2-, and 32.5% of 3-cyclohexene carboxylates.

Irradiation Induced Iron Carbonyl Catalyzed Isomerization of Alkenyl Ethers.—An example of these reactions is the isomerization of methyl 4-pentenyl ether. To a solution of 1.0 g (0.01 mol) of methyl 4-pentenyl ether in 135 ml of deoxygenated pentane, was added 0.1 g (0.07 ml, 5×10^{-4} mol, ~5 mol %) of iron pentacarbonyl. The solution was irradiated with a 200-W high pressure mercury lamp (Type S, 654A-36 Hanovia lamp, Engelhard Hanovia, Inc., Newark, N. J.) with argon bubbling through the solution for a 3-hr period. At 1-hr intervals, the irradiation was stopped and 3-ml samples were withdrawn and analyzed by infrared and gas chromatography after removal of most of the pentane by distillation. Infrared bands at 6.0, 8.0, and 10.7 μ indicated that within 1 hr most of the starting material had been converted into methyl *cis* and *trans* 1-pentenyl ethers. Analysis by gas chromatography showed two peaks of relative area 1:2.66. After 3 hr, an additional 5% of iron pentacarbonyl was added and the solution irradiated for 3 more hr. No change in infrared or gas chromatography analyses was detected after this period. The mixture was filtered to remove insoluble metal carbonyls and pentane solvent was removed by distillation. The total of 900 mg (~97%) of unpurified product was recovered. Gas chromatography analysis of this product indicated 97% of this mixture was methyl pentenyl ether isomers.

During some of the reactions a dark film was deposited on the immersion well of the reactor, decreasing the transmittance of ultraviolet light. The isomerization reactions were stopped when this occurred, the well was cleaned with sulfuric acid, and the reactions were continued.

Registry No.—Iron pentacarbonyl, 13463-40-6.

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The Total Synthesis of (±)-1-Deaza-1-thiareserpine[1a]

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The potential antihypertensive, (±)-1-deaza-1-thiareserpine (**10**), is described by way of its seven-step synthesis from the methyl ester of (±)-2α-methoxy-3β-hydroxy-5-ene-7-keto-1,2,3,4,7,8-*cis*-9α,10α-octahydro-1β-naphthoic acid, 4,3,4,5-trimethoxybenzoyl chloride (**5**), and 6-methoxy,3-(2-aminoethyl)benzo[*b*]thiophene (**3**).

Reserpine, isolated from *Rauwolfia serpentina* Benth, has been used clinically for a number of years as an antihypertensive. Its adverse side effects, together with our continuing interest in the field of sulfur-containing pharmaceuticals, has prompted our synthesis of a modified reserpine in which the indole nitrogen is replaced by the thianapthyl sulfur, *viz.* 1-deaza-1-thiareserpine (**10**).

The brilliant total synthesis of the natural reserpine molecule by Woodward and his coworkers[2] formed the basis of our synthetic development. Advantage was taken of other more recent work[3] to reduce the number of individual steps in our total synthesis of thiareserpine.

Since the benzo[*b*]thiophene molecule follows closely much of the electrophilic substitution chemistry of indole,[4] it was anticipated that the reactions to effect condensation of the molecules shown in Scheme I would proceed without difficulty and yield intermediates of unambiguous structures.

Thus, our initial synthetic attempts were directed toward the preparation of the previously unknown 6-methoxy-3-(2-aminoethyl)benzo[*b*]thiophene (**3**). Earlier work in our laboratories indicated that a feasible synthesis of this amine would be difficult by direct replacement of intermediate substituents on the thianapthene nucleus.[5] Therefore, the desired precusor, **3**, was formed by building the thiophene ring onto the benzene ring (Scheme II). Ethyl 4-chloro-3-ketobutyrate was treated with *m*-methoxybenzenethiol in pyridine to form the sulfide, **1**, which on ring closure with polyphosphoric acid and subsequent ammonolysis gave a mixture of 6-methoxy- and 4-methoxythianapthenes in a 20:1 ratio. Separation of the isomers was accomplished by fractional crystallization. The structure of the desired amide, **2**, 6-mehtoxy-3-thianaphthyl acid, was established by hydrolysis to its corresponding acid, followed by Raney

(1) (a) Presented in part at the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967. (b) To whom all correspondence should be addressed at the Institute of Biology and Medicine, Department of Chemistry. (c) Abstracted in part from the Master's Dissertation of G. P. Nilles and the Doctoral Dissertation of R. L. Titus.

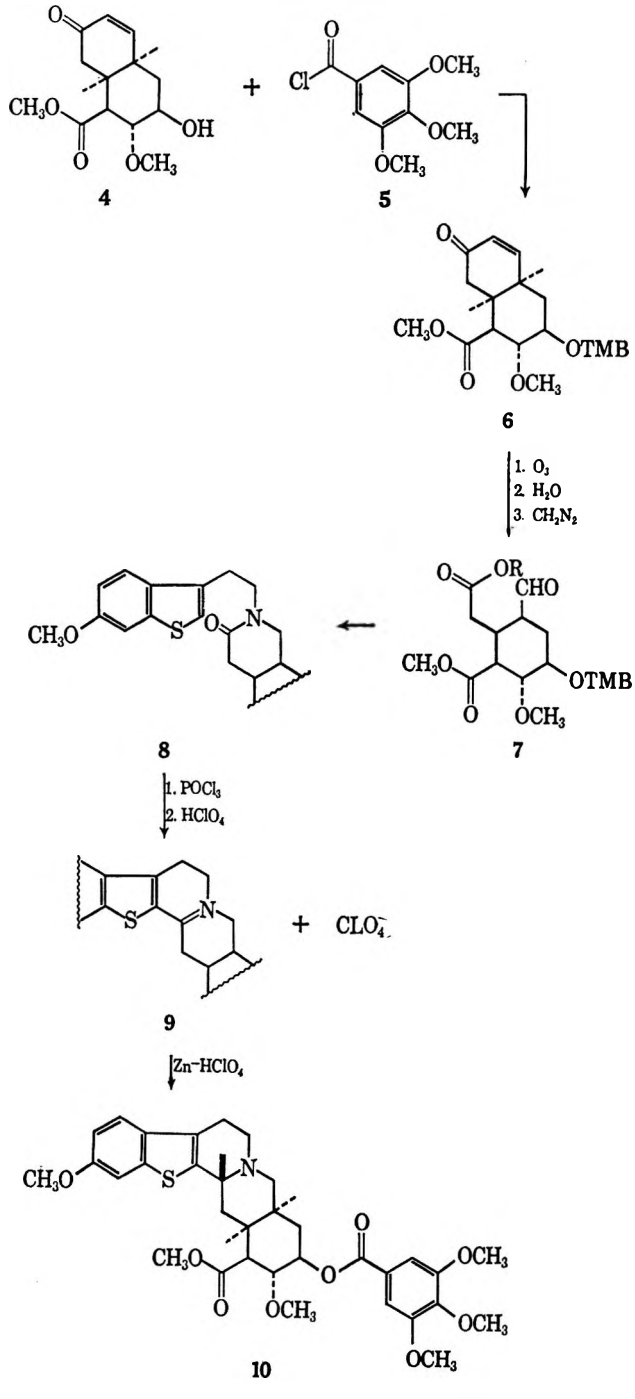
(2) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, **2**, 1 (1958).

(3) For examples see E. Schlittler in "The Alkaloids," Vol. 8, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1965, Chapter 13.

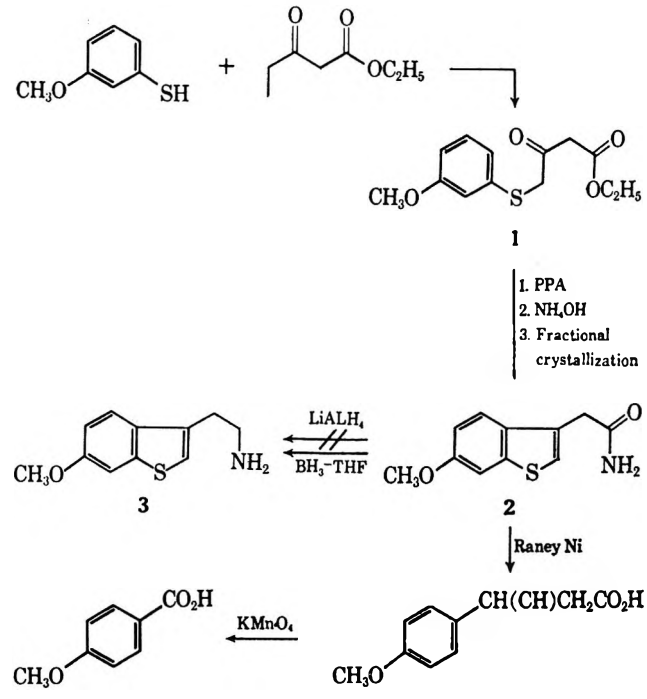
(4) G. V. Zyl, C. J. Bredeweg, R. H. Rynbrandt, and D. C. Neckers, *Can. J. Chem.*, **44**, 2283 (1966).

(5) R. L. Titus, Doctoral Dissertation, Michigan State University, East Lansing, Mich., 1964.

SCHEME I



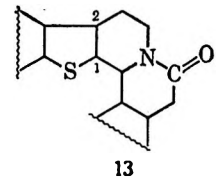
SCHEME II



nickel desulfurization to yield β-(methoxyphenyl)butyric acid, whose nmr spectrum showed a doublet at τ 8.7 (J = 7Hz) for the branched methyl group. Oxidation of the latter acid formed the known p-anisic acid. The 6-methoxy- and 4-methoxy-3-thianapthylacetic acids formed by saponification of the corresponding amides were submitted for evaluation as plant growth stimulants. The 4-methoxy compound was found to be only slightly less active than indole-3-acetic acid in *Avena* species. The 6-methoxy isomer was inhibitory at concentrations up to 10^{-5} M at which concentration it was slightly active as a growth promoter.[6]

Lithium aluminum hydride reduction of **2** failed to yield the amine[5] **3**; however, on treatment with borane–tetrahydrofuranate[7] a practicable yield of **3** was obtained.

Compound **4** prepared by Woodward's procedure[2] was treated with **5** to yield the diester acid **6** as shown in Scheme I. A previous publication[8] had shown the feasibility of forming **7** (R = H) directly from **6** by ozonolysis. Application of this process led to the aldehyde **7** (R = H). It was characterized as the previously unknown 2,4-dinitrophenylhydrazone. Treatment of **7** (R = H) with diazomethane led to the triester **7** (R = CH_3), which was condensed with **3** to give an imine. The imine on reduction with sodium borohydride readily gave the lactam **8** *via* internal ammonolysis. The formation of a 1,2,3,4-tetrahydrobenzothieno[2,3-*c*]pyridine system *via* a Pictet–Spengler-type condensation (**11**) was ruled out on the basis of elemental analysis (the desired lactam **8** has C–H



13

(10.091:1); structure **11** has C–H (10.626:1, found 10.133:1), stability of the yellow imine precursor in solution and a previous report[9] that condensations of this type lead to the desired system. A Bishler–Napieralski-type ring closure of the amide followed by treatment with perchloric acid gave the highly fluorescent (±)-1-deaza-1-thia-3,4-dehydroreserpine perchlorate (**9**). When subjected to reduction by zinc in perchloric acid, the desired (±)-1-deaza-1-thiareserpine (**10**) resulted. It was shown to be homogeneous by thin layer chromatography on alumina. That the C-3

(6) Complete details concerning these compounds as well as other 3,6- and 3,4-dissubstituted thianaphthenes are described in a publication: R. D. Schuetz and R. L. Titus J. *Heterocycl. Chem.*, **4**, 465 (1967).

(7) H. C. Brown and P. Heine, *J. Amer. Chem. Soc.*, **86**, 3566 (1964).

(8) J. Weichet, K. Pelz, and L. Bláha, *Collect. Czech. Chem. Commun.*, **26**, 1529 (1961).

(9) J. Jirkovsky and M. Protiva, *ibid.*, **28**, 2577 (1963).

hydrogen possessed the β configuration was shown by an extension of the work of Wenkert[10] and Protiva.[9] Wenkert found that epiallo yohimbanes, such as reserpine, do not have an absorption at 2740 cm^{-1}, while the allo systems (*i.e.*, the C-3 epimer) do. Protiva[9] in his synthesis of (±)-1-deaza-1-thiadeserpidine showed this system also lacked this absorption, while the C-3 epimer (α hydrogen) absorbed at 2760 cm^{-1}. The infrared spectrum of (±)-1-deaza-1-thiareserpine does not have this absorption. Further support of the stereochemistry comes from a publication by Vellux,[11] that zinc–perchloric acid reduction of the immonium salt in his synthesis of reserpine led exclusively to the C-3 hydrogen being β oriented.

By obtaining this "thiareserpine" in an over-all yield at 0.2% it is hoped that a new useful pharmaceutical is at hand. Work toward establishing its pharmacologic response will be undertaken and reported subsequently.

Experimental Section

Melting points were taken with an electrothermal melting point apparatus calibrated with furnished standards. Ultraviolet spectra were determined on a Beckman DK-2A instrument in 95% ethanol. Infrared spectra were run on a Perkin-Elmer 237B grating spectrophotometer.

Ethyl 4-(*m*-Methoxyphenylmercapto)-3-oxobutyrate (1).—A mixture of 35.8 g (0.256 mol) of *m*-methoxybenzenethiol[12] in 180 ml of pyridine cooled to 0° was treated in a dropwise manner with 41.9 g (0.256 mol) of ethyl 4-chloro-3-ketobutyrate maintaining the reaction temperature below 25–30°. After heating to 70–80° for 10 min and then recooling, the reaction solution was adjusted to pH 5 with 6 *N* hydrochloric acid. The resulting oil was separated and combined with the ether extracts (two 50-ml portions) of the aqueous layer. Removal of the solvent gave 62.4 g (0.233 mol, 91.0%) of the crude product.

Ethyl 6-(4)-Methoxythianaphthyl-3-acetate.—A mixture of 30.6 g (0.114 mol) of crude **1**, 50 ml of 85% orthophosphoric acid, and 100 g of phosphorus pentoxide in 200 ml of chlorobenzene was refluxed for 3 hr. The chlorobenzene was decanted and replaced with 200 ml of benzene, and the mixture underwent reflux for 3 hr. The combined aromatic solvents were washed successively with 10% sodium bicarbonate (50 ml) and water (two 50-ml portions). Removal of the solvents gave 25.6 g (0.120 mol, 90.5%) of the mixed esters which were used directly in the next step of the synthesis.

6-(4)-Methoxythianapthyl-3-acetamide (2).—The mixed esters, 17.0 g (0.0692 mol), were stirred continuously for 7 days in 400 ml of concentrated ammonium hydroxide at room temperature. The gummy amide was crystallized from hot ethanol and recrystallized to yield 4.82 g (0.0218 mol, 31.7%), mp 192–193°, of the pure 6-methoxy isomer as the less soluble product. Chromatography of the mother liquor residue, from the above fractional crystallization, on a 3 × 45 cm alumina column (Matheson activated alumina, 80–200 mesh, dried at 200° for 18 hr) after elution with chloroform and collection in 50-ml fractions gave the 4-methoxy isomer in fractions 10–13. It was recrystallized from a small amount of ethanol to give 0.24 g of product, mp 199–200°. Desulfurization of the 6-methoxy product with Raney nickel in the usual manner, followed by oxidation of the product with potassium permangamate, gave only *p*-anisic acid (by melting point determination and infrared analysis) as the product.

Anal. Calcd for $C_{11}H_{11}O_2NS$: C, 59.72; H, 5.01; N, 6.36; S, 14.47. Found for 6-methoxyamide: C, 60.21; H, 5.14; N, 6.22; S, 14.37. Found for 4-methoxyamide: C, 59.83; H, 5.08; N, 6.47; S, 14.42.

6-Methoxy-3-(2-aminoethyl)benzo[*b*]thiophene (3).—To a cold (0°) stirred 1 *M* solution of boran–tetrahydrofuranate (Metal Hydrides, Inc., Beverly, Mass., 40 ml, 0.040 mol) was added 1.10 g (5.00 mmol) of **2** in a single portion under nitrogen pressure. Following 8 hr of refluxing, the reaction mixture was set aside at room temperature for 16 hr and then 20 ml of 6 *N* hydrochloric acid was carefully added to the mixture. Removal of the tetrahydrofuran under reduced pressure, basification to a pH of 10 with 5 *M* sodium hydroxide, extraction with three 50-ml portions of ether, and removal of the ether gave the desired amine. The amine was distilled to yield 0.636 g (3.08 mmol, 61.4%), bp 130–140° (0.3 torr), $n^{25}D$ 1.5964. The amine was protected from atmospheric carbon dioxide by storage under nitrogen. A picrate was prepared in the usual manner and recrystallized three times from ethanol, mp 177–178°.

Anal. Calcd for $C_{17}H_{16}N_4SO_8$: C, 46.78; H, 3.69; N, 12.84; S, 7.35. Found: C, 46.60; H, 4.26; N, 12.77; S, 7.31.

(±)-2α-Methoxy-3β-(3′,4′,5′-trimethoxybenzyloxy)-5-ene-7-keto-1,2,3,4,7,8-*cis*-9α-10α-octahydro-1β-naphthoic Acid Methyl Ester (6).—From 0.500 g (1.98 mmol) of **4**[2,13] 0.701 g (1.50 mmol, 79.0%) of **6** was prepared, employing the method of Veichet, Pelz, and Bláha.[8] The product had bands at λ_{max} 217 mμ (ε 38,300) and 268 mμ (ε 10,900).

(±)-1-Deaza-1-thia-2,3-seco-3-oxoreserpine (8).—A 224-mg (0.500 mmol) quantity of **6** was ozonized in 10 ml of anhydrous methylene chloride using 1% O_3 in O_2 and employing 5% aqueous potassium iodide as an external indicator. The reaction mixture, following ozonolysis, was purged with dry nitrogen for 10 min and then heated at reflux for 45 min, under nitrogen, with 2 ml of water containing 0.01 g of hydroquinone. After separating the layers and extracting the aqueous layer with two 5-ml portions of methylene dichloride, the solvents were combined and dried with sodium sulfate. A 2,4-dinitrophenylhydrazone prepared at this point was recrystallized three times from ethanol, mp 128–131°.

Anal. Calcd for $C_{28}H_{32}O_{14}N_4$: C, 51.88; H, 4.97. Found: C, 51.60; H, 5.10.

The methylene chloride solution of **7** (R = H) was cooled to 0° and treated with a slight excess of ethereal diazomethane. After 10 min, half of the solvent was removed at reduced pressure under nitrogen. After recooling to 0°, a solution of 104 mg (0.503 mmol) of **3** in 1.4 ml of benzene was added in a single portion. After 10 min the yellow orange solution was treated at 0° with 19.0 mg (0.500 mmol) of sodium borohydride in 2 ml of anhydrous methanol during a period of 5 min. Acetic acid was added (two drops) and all solvents were removed under nitrogen at water pump pressure and finally with an oil pump at 0.01 torr. The thoroughly dried lactam **8** was purified by repetitive precipitation from ethyl acetate by adding ether to yield 240 mg (0.374 mmol, 74.8%), mp 145–148° dec (sealed capillary). The ultraviolet spectrum showed λ_{max} at 214 mμ (ε 51,100), 244 shoulder (15,600), and 267 (15,600).

Anal. Calcd for $C_{33}H_{33}O_{10}NS$: C, 61.76; H, 6.12; S, 5.00. Found: C, 61.51; H, 6.07; S, 4.67.

(±)-1-Deaza-1-thia-3,4-dehydroreserpine Perchlorate (9).—A solution of 100 mg (0.156 mmol) of **8** in 2 ml of freshly distilled phosphorous oxychloride was heated at 65° under nitrogen for 45 min. After removal of the solvent at water pump pressure, the reaction mixture was taken to dryness at 0.01 torr. The residue, dissolved in 4 ml of acetone, was treated with 3.5 ml of 0.1 *N* perchloric acid. The acetone was removed under a reduced nitrogen atmosphere and the aqueous suspension was extracted three times with 5-ml portions of chloroform. After drying the combined extracts with sodium sulfate, the solvent was removed to dryness. The residue was triturated with ether and collected to yield 101 mg (0.140 mmol, 89.8%) of **9**. For analysis it was recrystallized from ethanol–acetone, 5:1, mp 203–205° dec (sealed capillary). The infrared spectrum (KI pellet) showed λ_{max} at 1720 (C=O) and 1600 mμ (C=$\overset{+}{N}$<); the ultraviolet spectrum showed λ_{max} at 213 mμ (ε 44,800), 269 (19,300), 382 (9780).

Anal. Calcd for $C_{33}H_{38}O_{13}NSCl$: C, 54.80; H, 5.29; N, 1.94; S, 4.43. Found: C, 54.28; H, 5.53; N, 2.07; S, 4.64.

(±)-1-Deaza-1-thiareserpine (10).—A 111-mg (0.153 mmol) quantity of **9** was dissolved in a mixture of 5 ml of acetone and 1.5 ml of 0.7 *N* perchloric acid along with sufficient tetrahydrofuran to form a clear solution. The mixture was stirred and heated at 70° under nitrogen, and 0.15 g of zinc dust was added. After 10 min of reaction a second 0.15-g portion of zinc dust was added and this addition was repeated after another 10 min of reaction.

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Following another 10 min of reaction the characteristic fluorescence of the immonium salt (9) had almost disappeared and the reaction mixture was cooled to room temperature. After filtration and basifying to a pH of 9 with concentrated ammonium hydroxide, 10 ml of chloroform was added. The layers were separated and the aqueous layer was extracted twice with 5-ml portions chloroform. The chloroform extracts were combined, dried with sodium sulfate, filtered, and evaporated under a reduced nitrogen atmosphere. The residue (71 mg) was triturated with 10 ml of boiling ethanol, filtered hot, and concentrated to 3 ml. With constant stirring, 15 ml of ether was added and the resulting precipitate (54 mg, 0.086 mmol, 56%) of (±)-1-deaza-1-thiareserpine was collected. A small quantity (~1 mg) was subjected to thin layer chromatography on Woelm activity II alumina elution with a mixture of chloroform–methanol–benzene (10:3:1)) and showed a single dark spot (R_f 0.65) under ultraviolet light. Recrystallization from ethanol–ether (9:1) gave an analytical sample (21 mg), mp 188–191° (sealed capillary), of fine, pure white crystals. The infrared spectrum of thiareserpine ($CHCl_3$) showed absorption at 3032, 2930, 2860, 1735, 1590, 1505, 1465, 1420, 1340, 935, 800, 720, 680 cm^{-1}. The ultraviolet spectrum had λ_{max} at 213 mμ (ε 58,700), 231 shoulder (27,100), 244 shoulder (20,200), 267 (22,200).

Anal. Calcd for $C_{33}H_{39}O_9NS$: C, 63.34; H, 6.28; N, 2.24. Found: C, 63.08; H, 6.75; N, 2.53.

Registry No.—4-Methoxythianaphthyl-3-acetamide, 14679-05-1; 6-methoxythianaphthyl-3-acetamide, 14679-06-2; **3**, 14679-07-3; picrate of **3**, 14679-49-3; 2,4-dinitrophenylhydrozone of **7** (R = H), 14679-08-4; **8**, 14745-99-4; **9**, 14679-09-5; **10**, 14679-10-8.

The Synthesis of Three Fully Acetylated Aldobiouronic Acid Methyl Esters, Including 6-*O*-(Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate)-tetra-*O*-acetyl-β-D-glucopyranose

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6-*O*-α-D-Glucopyranuronosyl-D-glucose (isomaltouronic acid) is a possible moiety in the capsular polysaccharide of *Diplococcus pneumoniae* Type II. The synthesis of its fully acetylated methyl ester starting from β-isomaltose octaacetate is described. Improvements in the syntheses of the fully acetylated methyl esters of 6-*O*-β-D-glucopyranuronosyl-D-glucose (gentiobiouronic acid) and 4-*O*-α-D-glucopyranuronosyl-D-glucose (maltouronic acid) are also reported.

The structure of the capsular polysaccharide of *Diplococcus pneumoniae* Type II has been under investigation for some time.[2-5] It is known that this antigenic capsular polysaccharide, S-II, contains terminal as well as intercatenary glucuronic acid residues. Recent additional findings[6] concerning the structure of S-II have clarified much about the type of linkages involved in this polysaccharide as well as some of the anomeric configurations. Still, the anomeric configuration of the intercatenary, presumably 1–6 linked, glucuronosylglucose is still open to question. Comparison of the inhibition of the antigen–antibody precipitation in the S-II–anti S-II system by isomaltouronic acid and gentiobiouronic acid could yield information about the anomeric configuration of this linkage. Similarly, the inhibition of the same system by maltouronic and cellobiouronic acids could shed light on the immunological importance of the anomeric configuration of the terminal glucuronosyl linkage.

The terminal uronic acid in S-II behaves unexpectedly, in that, although the molecule has terminal cellobiouronic acid units,[6] rabbit serum obtained against a synthetic antigen containing this acid as terminal side chains will not agglutinate cells of *D. pneumoniae* Type II, although this serum will agglutinate cells of *D. pneumoniae* Type III or VIII,[7] even though the latter two types only have *intercatenary* cellobiouronic acid.[8-10] It appears that the immunological specificity attributable to the terminal acid group in S-II does not seem to be very sensitive to the fact that the acid is glycosidically linked to glucose by a β linkage.

Work on the serological inhibition reaction now in progress in collaboration with Dr. M. Heidelberger, might be expected to shed light on this point and will be reported elsewhere.

The synthesis of 6-*O*-α-D-glucopyranuronosyl-D-glucose (isomaltouronic acid), was initiated starting from 6-*O*-[α-D-glucopyranosyl]-β-D-glucopyranose octaacetate (β-isomaltose octaacetate) (**1**) which was obtained from the acid reversion of glucose following the method of Wolfrom and Thompson.[11] It was deacetylated and tritylated at the 6′ position in pyridine solution. Without further isolation, it was then acetylated and the resulting hepta-*O*-acetyl-6′-*O*-tritylisomaltose (**2**) was isolated by chromatography on silica gel in 61.5% yield. The nmr spectrum indicated that **2** was a mixture of α and β anomers, a finding that was expected, as tritylation in pyridine prior to acetylation would cause anomerization. Detritylation of **2** by brief treatment in acetic acid with 1 mol equiv of hydrogen bromide[12] gave 1,2,3,4,2′,3′,4′-hepta-*O*-acetylisomaltose (**3**) in 83% yield. The heptaacetate **3** was then oxidized with potassium permanganate in acetic acid, and the car-

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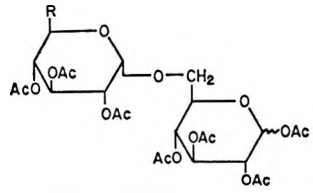
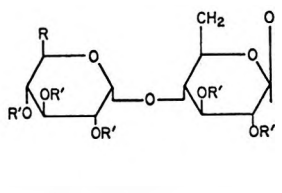
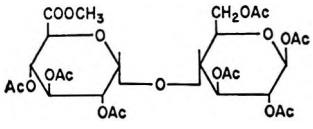
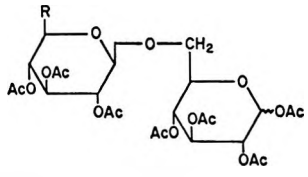




1, R = CH_2OAc (β 1-O-acetyl)
2, R = CH_2O trityl
3, R = CH_2OH
4, R = $COOCH_3$
5, R = $COOCH_3$ (β 1-O-acetyl)
6, R = CH_2OAc; R′ = Ac
7, R = CH_2O trityl; R′ = COC_6H_5
8, R = CH_2OH; R′ = COC_6H_5
9, R = COOH; R′ = COC_6H_5
10, R = $COOCH_3$; R′ = COC_6H_5



11



12, R = CH_2O trityl
13, R = CH_2OH
14, R = $COOCH_3$ (β 1-O-acetyl)

boxylic acid produced was directly esterified with diazomethane to give methyl hepta-*O*-acetylisomaltouronate (**4**) in 58% yield, showing that acetyl migration[13] in 1,2,3,4,2′,3′,4′-hepta-*O*-acetylisomaltose is insignificant under these conditions. This compound, a mixture of the α and β anomers, could not be induced to crystallize. Consequently, **4** was converted into the 1-bromo derivative, hepta-*O*-acetylisomaltouronosyl bromide methyl ester, which was treated with silver acetate in benzene according to Wolfrom and Fields[14] to give crystalline methyl hepta-*O*-acetyl-β-D-isomaltouronate (**5**) in 66% yield.

The synthesis of maltouronic acid, 4-*O*-α-D-glucopyranuronosyl-D-glucose, was first reported by Hirasaka,[15] who subjected benzyl β-maltoside to catalytic oxidation. That the C-6′, rather than the C-6, position was attacked, may probably be attributed to steric hindrance of C-6 by the phenyl group at C-1. Since the removal of small amounts of the C-6 oxidized material may prove cumbersome, and since the presence of such an impurity might cloud results of immunochemical tests, we used an alternative route for the preparation of **11** analogous to that used by Lindberg and Selleby[16] for the preparation of cellobiouronic acid. 1,6-Anhydro-4-*O*-α-D-glucopyranosyl-β-D-glucopyranose hexaacetate was prepared *via* phenyl β-maltoside by the procedure of Lindberg.[17] The hexaccetate (**6**) was deacetylated, monotritylated, and then benzoylated to yield crystalline 1,6-anhydro-4-*O*-(6′-*O*-trityl-α-D-glucopyranosyl)-β-D-glucopyranose pentabenzoate (**7**) in 54% yield. Next, **7** was reductively detritylated with hydrogen over palladium black to give, after purification by chromatography over silica gel, 1,6-anhydro-2,3,2′,3′,4′-penta-*O*-benzoylmaltose (**8**) as colorless needles in 92% yield. When **8** was oxidized with potassium permanganate in glacial acetic acid, the product, 1,6-anhydropenta-*O*-benzoylmaltouronic acid (**9**), was obtained in crystalline form, also in 92% yield. Reaction of **9** with diazomethane yielded crystalline methyl 1,6-anhydropenta-*O*-benzoylmaltouronate (**10**). Treatment of **9** with sodium methoxide and subsequent acid-catalyzed hydrolysis of the deacetylated **9** with aqueous 0.5 *N* sulfuric acid gave a product from which amorphous maltouronic acid was isolated in 48% yield by cellulose chromatography. Its rotation is in excellent agreement with the one reported previously, while the derived methyl hepta-*O*-acetyl-β-D-maltouronate (**11**) also has constants in close agreement with the ones reported.[18] Of course it has previously been established that, especially in hexuronosyl hexoses, the 1,6-anhydro bridge may be opened without hydrolysis of the intersaccharidic linkage.[16,19,20]

Gentiobiouronic acid was first synthesized by Hotchkiss and Goebel.[21] These workers obtained the aldobiouronic acid by Koenigs–Knorr condensation of methyl acetobromoglucuronate with 1,2,3,4-tetra-*O*-acetyl-β-D-glucose. The synthesis reported here starts from 6-*O*-[β-D-glucopyranosyl]-D-glucose (gentiobiose) and takes a course analogous to that of our synthesis of isomaltouronic acid. Gentiobiose was monotritylated in pyridine solution. The reaction could be conveniently followed by thin layer chromatography on Avicel microcrystalline cellulose.[22] After the completion of the reaction, the compound was acetylated *in situ* and purified by chromatography on silica gel to give 1,2,3,4,2′,3′,4′-hepta-*O*-acetyl-6′-*O*-tritylgentiobiose (**12**) in 55% yield as a mixture of the anomeric acetates, as shown by its nmr spectrum. Detritylation of **12** was achieved by brief treatment with 1 mol equiv of hydrogen bromide[12] to give crystalline 1,2,3,4,2′,3′,4′-hepta-*O*-acetylgentiobiose (**13**), a mixture of anomers as shown by its nmr. Potassium permanganate oxidation of **13** in acetic acid solution gave hepta-*O*-acetylgentiobiouronic acid which was esterified directly with diazomethane to yield crystalline methyl hepta-*O*-acetylgentiobiouronate in 50% yield. The material, although crystalline, was shown by nmr spectroscopy to be a mixture of anomeric acetates. Treatment of this ester with hydrogen bromide in acetic acid, followed by reaction of the 1-bromo derivative with silver acetate in benzene,[14] gave, in 50% yield, crystalline methyl hepta-*O*-acetyl-β-D-gentiobiouronate (**14**) identical in melting point and optical rotation with that obtained by Hotchkiss and Goebel.[21]

A few comments concerning the nmr spectra of some of the intermediates are in order. The spectrum of β-isomaltose octaacetate (**1**) with its H-1 showing as a doublet at τ 4.2 ($J_{1,2}$ = 8 Hz) had signals for six protons in the region τ 5.7–6.4. Obviously they were two H-6′, two H-6, H-5′, and H-5 protons. On the basis of higher deshielding effect of an –OAc compared to an –*O*-glycosyl group, the broad signal at τ 5.8 was assigned to two H-6′ protons and that at 6.23 was assigned to two H-6 protons. When the 6′-*O*-acetyl group was removed, as in the hepta-*O*-acetate **3**, the signal at τ 5.8 of compound **1** shifted to 6.38, undoubtedly owing to the removal of this more de-

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shielding moiety. The anomeric acetates of methyl isomaltouronate (**4**) showed doublets centered at τ 3.76 and 4.33 for α and β diastereoisomers, respectively, in close resemblance to the heptaacetate **3** which is also a mixture of two anomers. In addition, the H-5′ of **4** was shifted downfield to τ 5.7 ($J_{4,5}$ = 10.5 Hz) owing to the deshielding effect of the –COOMe group. The CH_3 of the methyl ester, appearing as a sharp singlet at τ 6.28, was overlapped with the two H-6 protons and the H-5 proton in about the same region. The spectrum of methyl hepta-*O*-acetyl-β-D-isomaltouronate showed only one anomeric hydrogen as a doublet at τ 4.35 ($J_{1,2}$ = 8.5 Hz).

The spectra of the gentiobiose series could be explained on a similar type of reasoning. The spectrum of 1,6-anhydro-6′-*O*-tritylpenta-*O*-benzoylmaltose (**7**) showed five benzoyl groups, one trityl group, and a two-proton signal at τ 6.60 along with other peaks. The signal at τ 6.60, which was assigned to two H-6′ hydrogens (shielded by the trityl group), was shifted to 6.16 when the trityl group was replaced by hydrogen as in compound **8**. The hydroxy compound **8** and the acid **9** which were crystallized from ether, showed exactly 1 mol of ether of crystallization in their nmr spectra. The acid **9** gave an ester with diazomethane which also gave a characteristic signal for the methyl ester in the nmr spectrum. Pure methyl hepta-*O*-acetylmaltouronate had a signal for H-1 at τ 4.20 as a doublet ($J_{1,2}$ = 8 Hz) and a singlet for the methyl ester at 6.23.

Experimental Section[23]

1,2,3,4,2′,3′,4′-Hepta-*O*-acetyl-6′-*O*-tritylisomaltose (**2**).—Crystalline β-isomaltose octaacetate (**1**, 10 g) was deacetylated with 0.03 *N* sodium methoxide in methanol for 2 hr. The reaction mixture was concentrated to dryness and pyridine was distilled off twice under vacuum. The residue was taken up in dry pyridine (200 ml) and tritylated with 15 g of tritylchloride with stirring for 3 days. Acetic anhydride (40 ml) was added and after 3 days the mixture was poured into ice water (1.5 l.) with stirring. The solid material was collected by filtration, dried under vacuum, dissolved in a small volume of benzene, and added to the top of a column of silica gel (400 g, Merck Darmstad 0.05–0.2 mm) which was eluted with benzene–ether (2:1). After removal of some triphenylcarbinol and higher tritylated derivatives there was obtained amorphous 8 g (61.5% yield) of 1,2,3,4,2′,3′,4′-hepta-*O*-acetyl-6′-*O*-tritylisomaltose (**2**), $[\alpha]^{20}D$ +100.2° (*c* 1, chloroform).

The nmr spectrum showed two doublets for H-1, centered around τ 3.68 and 4.26, indicating the presence of both α- and β-acetates. The spectrum had a general resemblance to **1** and also confirmed the presence of one trityl group in the molecule.

Anal. Calcd for $C_{45}H_{50}O_{18}$: C, 61.50; H, 5.73. Found: C, 61.72; H, 5.68.

1,2,3,4,2′,3′,4′-Hepta-*O*-acetylisomaltose (**3**).—A solution of **2** (4.5 g) in acetic acid (30 ml) was treated for 2 min with a solution of hydrogen bromide (0.4 g) dissolved in acetic acid (10 ml), while shaking vigorously. The mixture was immediately filtered through a sintered glass funnel into ice water (300 ml), and the heptaacetate was extracted with four 100-ml portions of chloroform. The extract was washed with water, saturated sodium bicarbonate, and, again, water. The solution was dried over magnesium sulfate and concentrated to dryness; the product was purified by chromatography on silica gel using benzene–ether (20:60). The pure 1,2,3,4,2′,3′,4′-hepta-*O*-acetylisomaltose (**3**) was obtained in a yield of 2.7 g, $[\alpha]^{20}D$ +117.8° (*c* 0.7, chloroform).

Anal. Calcd for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 49.10; H, 5.66.

6-*O*-(Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate)-tetra-*O*-acetyl-β-D-glucopyranose (**5**).—To a solution of **3** (1.9 g) in acetic acid (20 ml), finely powdered potassium permanganate (1.3 g) was added slowly with stirring at room temperature for 5 days, at which time thin layer chromatography on silica gel G (benzene–ether–acetic acid, 33:66:2.5) showed the reaction to be nearly complete. Excess permanganate was destroyed with sodium oxalate, and the mixture was poured into water (250 ml). The acid was extracted with five 80-ml portions of chloroform, and the extract was washed with water, dried over magnesium sulfate, and concentrated to a white amorphous foam. This product was esterified in methanol solution with diazomethane in ether and purified by chromatography over silica gel, using benzene–ether (1:2), to yield methyl hepta-*O*-acetylisomaltouronate (**4**, 1.15 g) as an anomeric mixture of the acetates as revealed by the nmr spectrum. The material could not be induced to crystallize. Consequently, **4** (0.6 g) was dissolved in 32% hydrogen bromide in glacial acetic acid (10 ml) and the mixture shaken at room temperature for 7 min. Chloroform was added and the solution was washed thrice with water, dried over sodium sulfate, and concentrated to dryness. It was taken up in dry benzene (50 ml), and silver acetate (6 g) was added. Stirring was continued for 16 hr after which solids were removed by filtration through Celite, and the filtrate was concentrated to dryness. The product was then purified by chromatography over silica gel, using benzene–ether (1:1) as the eluent. From ethanol, pure 6-*O*-(methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate)tetra-*O*-acetyl-β-D-glucopyranose (**5**) was obtained as fine needle-shaped crystals: mp 169–170°; $[\alpha]^{20}D$ +96.1° (c 0.5, chloroform).

The nmr spectrum showed a signal for H-1 at τ 4.35 and the signal at 6.28 for the methyl ester.

Anal. Calcd for $C_{27}H_{36}O_{19}$: C, 48.80; H, 5.46. Found: C, 48.66; H, 5.41.

1,6-Anhydropenta-*O*-benzoyl-6′-*O*-tritylmaltose (**7**).—A 6.7-g sample of 1,6-anhydromaltose hexaacetate[17] (**6**) was deacetylated in 0.03 *N* barium methoxide. The product was dissolved in pyridine (140 ml) and trityl chloride (5.7 g) was added. After 3 days benzoyl chloride (16 g) was added while cooling, and the reaction mixture was left at room temperature overnight. Methanol (10 ml) was added, and after 0.5 hr the solution was concentrated at 40° under vacuum to about 30 ml. Chloroform (200 ml) was added, and the solution was washed thrice with water and dried over magnesium sulfate. Concentration, followed by dissolution of the residue in ethyl acetate (30 ml) and ethanol (100 ml), gave crystalline 1,6-anhydropenta-*O*-benzoyl-6′-*O*-tritylmaltose (**7**), mp 230–231°. From the mother liquor, an additional 2 g was recovered after chromatography over silica gel (benzene–ether, 7:3) for a total yield of 6.8 g (54%) of **7**, $[\alpha]^{20}D$ +49° (*c* 1.0, chloroform).

Anal. Calcd for $C_{66}H_{56}O_{15}$: C, 72.78; H, 5.18. Found: C, 72.67; H, 5.22.

1,6-Anhydro-2,3,2′,3′,4′-penta-*O*-benzoylmaltose (**8**).—Palladium chloride (1.2 g) was added to a solution of the trityl compound **7** (6.2 g) dissolved in dioxane (150 ml, purified by passage through a column of aluminum oxide, Brockman Grade I) and the suspension was stirred under hydrogen at atmospheric pressure for 18 hr. Silver carbonate (4 g) was added and the solids were removed by filtration. The filtrate was concentrated and chromatographed over silica gel using chloroform–ether (9:1) as the eluent. After pooling of the correct fractions, they were concentrated and dissolved in ether. Crystallization was almost immediate. A yield of 4.8 g (92%) of 1,6-anhydro-2,3,2′,3′,4′-penta-*O*-benzoylmaltose was obtained: mp 136–138°; $[\alpha]^{20}D$ +53.6° (*c* 0.85, chloroform). The nmr spectrum showed the presence of exactly 1 mol of ether of crystallization. Tritylation of **8** yielded the original 6′-*O*-trityl derivative **7**.

Anal. Calcd for $C_{47}H_{40}O_{15}O\cdot(C_2H_5)_2$: C, 66.66; H, 5.48. Found: C, 66.53; H, 5.66.

1,6-Anhydropenta-*O*-benzoylmaltouronic Acid (**9**).—The detritylated compound **8** (4.6 g) dissolved in glacial acetic acid (45 ml) was oxidized with potassium permanganate (3 g) for 3 days as described for **4**. The product, which was obtained as a colored syrup (4.3 g, 92%), was purified by chromatography over silica gel, using chloroform–ether–acetic acid (3:3:0.2) as the eluent. From ether, crystals were obtained which contained

(23) All melting points are corrected. Nmr spectra were taken in $CdCl_3$ on a 60-Mc Varian Instrument using tetramethylsilane as an internal reference. Elemental analyses were performed by the Section on Analytical Services and Instrumentation of this laboratory, for which we wish to express our graditude.

1 mol of ether of crystallization, as shown by its nmr spectrum. The 1,6-anhydropenta-*O*-benzoylmaltouronic acid (**9**) has mp 152–153°, $[\alpha]^{20}D$ +46° (*c* 0.4 chloroform).

Anal. Calcd for $C_{47}H_{38}O_{18}\cdot O(C_2H_5)_2$: C, 65.66; H, 5.19. Found: C, 65.98; H, 4.90.

Treatment of **9** with diazomethane in the usual fashion gave the methyl ester (**10**), mp 169–171°.

4-*O*-(Methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate)-tetra-*O*-acetyl-β-D-glucose (**11**).—The crystalline acid **9** (3.5 g) was debenzoylated in 0.05 *N* sodium methoxide solution (60 ml) for 2 hr. The solution, after neutralization with Amberlite IR-120 exchange resin, was freed from methyl benzoate. The deacetylated product was heated at 95–100° in 0.5 *N* aqueous sulfuric acid for 12 hr. After neutralization with barum carbonate, and removal of cations by ion exchange, the product was isolated by chromatography over cellulose, using ethyl acetate–acetic acid–water (18:7:8) as the eluent to yield 650 mg (48%) of 4-*O*-α-D-glucopyranuronosyl-D-glucose (maltouronic acid), $[\alpha]^{20}D$ +115° (*c* 0.17, water). Dutton and Slessor[18] have reported $[\alpha]^{20}D$ +116° for this acid. The derived 4-*O*-(methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranosyluronate)tetra-*O*-acetyl-β-D-glucose (**11**), prepared by esterification of maltouronic acid with diazomethane followed by acetylation with sodium acetate and acetic anhydride and crystallization from ethanol, had mp 199–200°, $[\alpha]^{20}D$ +71° (*c* 0.72 chloroform).

Anal. Calcd for $C_{27}H_{36}O_{19}$: C, 48.80; H, 5.46. Found: C, 48.95; H, 5.58.

1,2,3,4,2′,3′,4′-Hepta-*O*-acetyl-6′-*O*-tritylgentiobiose (**12**).—Gentiobiose (8 g) was tritylated in pyridine solution and then acetylated *in situ* as described in the preparation of **2**. The hepta-*O*-acetyl-6′-*O*-tritylgentiobiose (**12**) (12.5 g) obtained had $[\alpha]^{20}D$ +38° (*c* 1.5, chloroform). The nmr spectrum showed the presence of both anomeric acetates.

Anal. Calcd for $C_{46}H_{50}O_{18}$: C, 61.50; H, 5.73. Found: C, 61.66; H, 6.03.

1,2,3,4,2′,3′,4′-Hepta-*O*-acetylgentiobiose (**13**).—In order to remove the trityl group from **12** (9 g) it was dissolved in acetic acid (60 ml) and treated with 1 equiv of hydrogen bromide exactly as described in the preparation of **3**. After purification by silica gel chromatography as described for **3**, the pure 1,2,3,4,2′,3′,4′-hepta-*O*-acetylgentiobioise (**13**), was crystallized from ethanol yielding 5.4 g (83%): mp 162–167°; $[\alpha]^{20}D$ +24.7° (*c* 1.0 chloroform).

Anal. Calcd for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 49.01; H, 5.81.

6-*O*-(Methyl-2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)-tetra-*O*-acetyl-β-D-glucopyranose (**14**).—Gentiobiose heptaacetate **13** (4 g), was dissolved in acetic acid (40 ml) and oxidized with potassium permanganate (2.7 g) exactly as described in the preparation of **4**. Direct esterification of the acid with diazomethane in ether gave 1.91 g (50%) of the desired 6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)tetra-*O*-acetyl-D-glucopyranose after purification by silica gel chromatography (benzene–ether, 1:2): mp 200–201° (after crystallization from methanol); $[\alpha]^{20}D$ −1.5° (*c* 1, chloroform).

Anal. Calcd for $C_{27}H_{36}O_{19}$: C, 48.80; H, 5.46. Found: C, 48.52; H, 5.36.

The above methyl ester, albeit crystalline, was still a mixture of anomeric acetates. It was therefore treated with hydrogen bromide, followed by silver acetate in benzene, as described for **5** to give 6-*O*-(methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranosyluronate)tetra-*O*-acetyl-β-D-glucose (**14**), in 50% yield: mp 200–202°, $[\alpha]^{20}D$ −11° (*c* 0.1, chloroform).

Registry No.—**2**, 15811-22-0; **3**, 15811-23-1; **5**, 15811-24-2; **7**, 15811-25-3; **8**, 15811-26-4; **9**, 15811-27-5; **10**, 15856-56-1; **11**, 4079-39-4; **12**, 15811-29-7; **13**, 15811-30-0; **14**, 15811-31-1.

Acknowledgment.—We wish to thank Mr. H. W. Diehl for assistance in the preparation of β-isomaltose octaacetate.

The Synthesis of 18,19-Dioxygenated Steroids by Intramolecular Radical Processes[1]

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Received October 10, 1967

By the application of known methods, especially intramolecular substitution reactions, pregnenolone has been converted into 18,19,20α- and 18,19,20β-trihydroxypregn-4-en-3-one. These compounds are possible metabolites from the perfusion of adrenal glands with progesterone.

The ability of adrenal tissue to oxygenate steroids at the angular methyl groups (C-18 and C-19) is well known.[2] Steroids functionalized at either of these positions have been isolated from adrenal tissue[2a–d] or formed by the action of adrenal preparations on exogenous steroidal substrates.[2e–g] These substances have been of considerable interest as a result of their intrinsic biological activity (aldosterone, for instance), their role in hormone biosynthesis (19-hydroxy steroids), and the chemical challenge inherent in their preparation. This challenge has been met by the development of several methods[3] for the selective functionalization of "unactivated" carbon atoms.

Although steroids substituted at either C-18 or C-19 are well known and now, for the most part, easily available, the occurrence of steroids functionalized at *both* angular methyls has not yet been reported. (Allusion has been made to functionalization at C-18 of a 19-substituted steroid. The nature of the products was not disclosed.[3g]) We now report the synthesis of the isomeric 18,19-disubstituted pregnanetriols **1a** and **1b**. This synthesis was undertaken as a portion of our continuing program of synthesis of 18- and 19-substituted steroids[4] and to provide standard materials for a program of adrenal perfusion. Compound

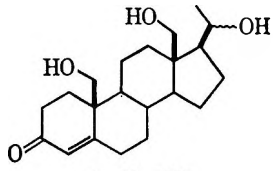
(1) Contribution No. 39 from the Research Institute for Medicine and Chemistry. For No. 38, see M. M. Pechet and H. F. Kohler, *J. Clin. Invest.*, in press. A preliminary description of this work was presented at the 149th National Meeting of the American Chemical Society, Chicago, April 1965, Abstract, p 4N.

(2) (a) S. A. Simpson, J. F. Tait, A. Wettstein, R. Neher, J. von Euw, O. Schindler, and T. Reichstein, *Helv. Chim. Acta*, **37**, 1163 (1954); (b) R. Neher and A. Wettstein, *ibid.*, **39**, 2062 (1956); (c) R. Neher, *Folia Endocrinologia* (Pisa), **8**, 55 (1960); (d) F. G. Peron, *Endocrinology*, **69**, 39 (1961); (e) H. Levy and S. Kushinsky, *Arch. Biochem. Biophys.*, **88**, 290 (1955); (f) P. S. Chen, H. P. Schedl, G. Rosenfeld, and F. C. Bartter, *Proc. Soc. Exptl. Biol. Med.*, **97**, 683 (1958); (g) F. G. Peron, *Endocrinology*, **70**, 386 (1962).

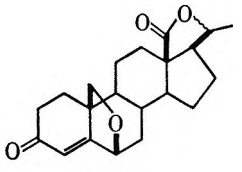
(3) (a) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, **82**, 2640 (1960); (b) P. Buchschacher, M. Cereghetti, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **42**, 2122 (1959); (c) G. Cainelli, M. L. Mihailovic, D. Arigoni, and O. Jeger, *ibid.*, **42**, 1124 (1959); (d) Ch. Meystre, K. Heusler, J. Kalvoda, P. Weiland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961); (e) E. J. Corey and W. R. Hertler, *J. Amer. Chem. Soc.*, **80**, 2903 (1958); (f) M. Akhtar, *Advan. Photochem.*, **2**, 263 (1964); (g) K. Heusler and J. Kalvoda, *Angew. Chem. Intern. Ed. Engl.*, **3**, 525 (1964).

(4) R. H. Hesse and M. M. Pechet, *J. Org. Chem.*, **30**, 1723 (1965).

1 was chosen as a synthetic goal, since, in our experience, C-20-reduced metabolites are often isolated after lengthy perfusion of the adrenal gland.[5]

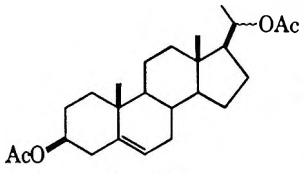


1a, 20α OH
b, 20β OH

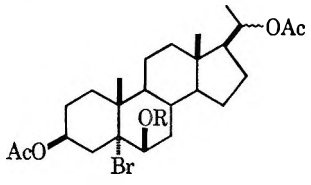


2a, 20α
b, 20β

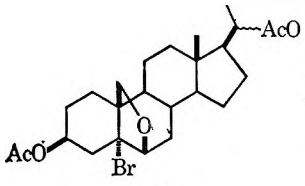
SCHEME I



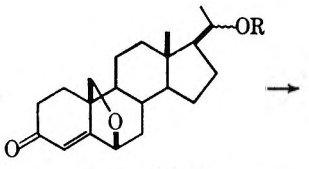
3a, 20α
b, 20β



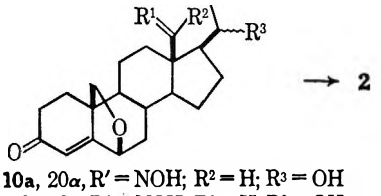
4a, 20α, R=H
b, 20β, R=H
5, 20β, R=NO



6a, 20α
b, 20β



7a, 20α, R=Ac
b, 20β, R=Ac
8a, 20α, R=H
b, 20β, R=H
9a, 20α, R=NO
b, 20β, R=NO



→ **2**

10a, 20α, R′=NOH; R²=H; R³=OH
b, 20β, R′=NOH; R²=H; R³=OH

11a, 20α, R′=  ; R² + R³=−O⁻

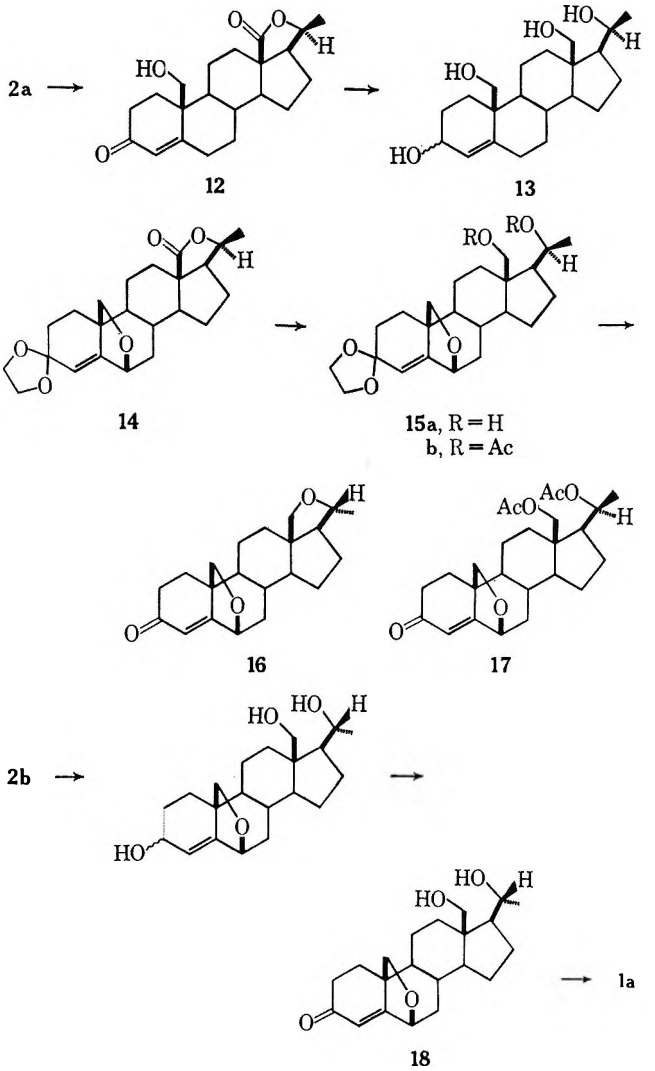
b, 20β, R′=  ; R² + R³=−O⁻

The key intermediate in each series was the corresponding 6,19-oxido-20-18-lactone **2**, which contains the requisite Δ⁴-3-keto system as well as potential hydroxyl groups at 18, 19, and 20. This compound was prepared from the readily available diacetates **3a** and **3b**[6] by the application of methods developed in these and other laboratories. Reaction of the diacetate **3** with hypobromous acid[7] gave the bromo alcohol **4**, which on irradiation in the presence of lead tetraacetate and iodine[3d] was converted into the epoxide **6** (Scheme I). The same epoxide was readily prepared by irradiation of the nitrite **5** in the presence of iodine.[8] Controlled saponification of **6** to remove the 3-acetate, followed by oxidation and β elimination,[7b] gave the Δ⁴-3-keto compound **7**. Alkaline hydrolysis of **7** gave the alcohol **8**, which on treatment with nitrosyl chloride afforded the nitrite **9**. Irradiation[3a] of **9** afforded the oxime **10**, which was treated with nitrous acid[9] to give the hemiacetal **11**. This compound was, without isolation, oxidized with chromium trioxide in acetone[10] to give the desired intermediate **2**.

It now remained to adjust the oxidation level of the substituents at C-6 and C-18. It is at this point that the synthesis of the isomeric triols **1a** and **1b** diverged.

Treatment of the oxidolactone **2a** with zinc and acetic acid[7b] gave the 19-hydroxy compound **12** (Scheme II). Reduction of this gave a material,

SCHEME II



12 **13** **14** **15a**, R=H **b**, R=Ac **16** **17** **18**

(5) We attribute this to reductases present in the blood used for perfusion; *cf.* R. V. Short, *J. Endocrinology* (London), **16**, 415 (1958).

(6) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(7) (a) Y. Ueno, *J. Pharm. Soc.* (Japan), **72**, 1622 (1952); (b) M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, **86**, 1528 (1964).

(8) M. Akhtar, D. H. R. Barton, and P. G. Sammes, *ibid.*, **86**, 265 (1964); **87**, 4601 (1965).

(9) S. G. Brooks, R. M. Evans, G. F. H. Green, J. S. Hunt, A. G. Long, B. Mooney, and L. J. Wyman, *J. Chem. Soc.*, 4614 (1958).

(10) K. Bowden I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *ibid.*, 39 (1946).

presumably the tetrol **13**, which was difficult to isolate and purify because of inconvenient solubility properties. Oxidation of **13** with manganese dioxide[11] might have been expected to afford the desired triol **1a**. In practice, however, the reaction was extremely sluggish, and this approach was abandoned when it was found that model 3,19-dihydroxy-Δ^4 steroids were incompletely and only with great difficulty oxidized by manganese dioxide. As an alternative, **2a** was converted into the cyclic ethylene ketal **14** and reduced with lithium aluminum hydride to give the diol **15a**. Treatment of **15a** with toluene-*p*-sulfonic acid removed the protecting group but apparently effected a concomitant cyclodehydration to give a nonhydroxylic compound formulated as **16**. The diacetate **15b**, however, underwent an uncomplicated deketalization to give the Δ^4-3-keto diacetate **17**, which on treatment with zinc and acetic acid gave the 18,21-diacetate of the desired triol **1a**. Hydrolysis under mild conditions proceeded cleanly to give the unprotected triol **1a**.

The observation in these laboratories that 3-hydroxy-Δ^4-6,19-oxido steroids are slowly[12,13] but cleanly converted into the 3-keto compounds by dichlorodicyanoquinone (DDQ)[14] made it possible to shorten this somewhat circuitous route (*vide supra*) during the preparation of the remaining triol **1b**. Reduction of the appropriate oxidolactone **2b** with lithium aluminum hydride gave a mixture of triols, which on oxidation with DDQ afforded the oxidodiol **18**. Happily, this compound was stable to acetic acid (*vide supra*) and upon reduction with zinc in that medium gave the desired triol **1b**.

Experimental Section

All melting points were obtained on the Kofler hot stage. Optical rotations are reported for 0.5–1% solutions in chloroform unless otherwise stated. Microanalyses were performed in the laboratories of Dr. Alfred Bernhardt, Max Planck Institute, Mülheim (Ruhr), Germany. All compounds had appropriate and unexceptional infrared spectra.

5α-Bromopregnane-3β,6β,20α-triol 3,20-Diacetate (4a).—A stirred solution of 3β,20α-dihydroxypregn-5-ene 3,20-diacetate (**3a**) (1 g) in dioxane (12 ml) containing aqueous perchloric acid (0.5 ml, 3%) was treated with N-bromoacetamide (950 mg, added in three portions at 10-min intervals). The reaction mixture was stirred for a further 30 min in the dark and then poured into ice water and treated with aqueous sodium sulfite (10%). The product was extracted into methylene chloride, which was then washed with sodium bicarbonate and water, dried, and concentrated *in vacuo*. Crystallization from petroleum ether (bp 30–40°) and methylene chloride gave the title compound (500 mg), mp 160–166°. The analytical specimen had mp 160–166°, $[\alpha]_D$ −49.5°.

Anal. Calcd for $C_{25}H_{39}O_5Br$: C, 60.12; H, 7.81; O, 16.03; Br, 16.04. Found: C, 60.24; H, 7.62; O, 15.94; Br, 16.14.

5α-Bromopregnane-3β,20α-diol 6β,19-Epoxide 3,20-Diacetate (6a).—A stirred solution of the bromohydrin **4a** (1 g) in dry benzene (75 ml) containing lead tetraacetate (2.5 g) and iodine (1.14 g) was irradiated for 17.5 hr using a 200-W lamp. After irradiation, the mixture was poured into water and the product extracted into ether. The organic extract was washed with aqueous sodium thiosulfate (10%) and water, dried, and evaporated to dryness. The title compound **6a** was crystallized from methanol (730 mg), mp 193–205°. The analytical sample had mp 203.5–206°, $[\alpha]_D$ −7.5°.

Anal. Calcd for $C_{25}H_{37}O_5Br$: C, 60.36; H, 7.46; O, 16.10. Found: C, 60.36; H, 7.69; O, 16.33.

5α-Bromopregnane-3β,20α-diol 6β,19-Oxide 20-Acetate.—A solution of the 3,20-diacetate **6a** (7.6 g) in ethanol–water (3.9 l., 3:1) containing sodium hydroxide (630 mg) and methanol (63 ml) was allowed to stand at 5° for 16 hr. After the addition of acetic acid, the mixture was concentrated to dryness *in vacuo*, partitioned between methylene chloride and water, and the organic phase filtered and taken to dryness. The residual solid was recrystallized from cyclohexane–methylene chloride to give the title compound in two crops: (i) 3 g, mp 198–204°, and (ii) 2.3 g, mp 192–204°. The analytical sample had mp 202–206°, $[\alpha]_D$ −10°.

Anal. Calcd for $C_{23}H_{35}O_4Br$: C, 60.66; H, 7.69; O, 14.07; Br, 17.78. Found: C, 60.68; H, 7.67; O, 14.11; Br, 17.70.

20α-Hydroxypregn-4-en-3-one 6β,19-Oxide 20-Acetate (7a).—A solution of 5α-bromopregnan-3β,20α-diol 6β,19-oxide 20-acetate (5.3 g) in acetone (300 ml) was treated with an excess of Jones reagent.[10] After 5 min, the excess oxidant was decomposed with methanol and the mixture partitioned between methylene chloride and half-saturated salt solution. After the usual work-up, a crude product was obtained which was dissolved in a solution of potassium acetate in methanol (500 ml) and heated under reflux for 0.5 hr. The solution was cooled, taken to dryness, and the residue partitioned between methylene chloride and water. The organic layer was worked up as usual to afford the title compound **7a** in two crops: (i) 1.4 g, mp 133–138°, and (ii) 2.7 g, mp 132–138°. The analytical sample crystallized from methanol had mp 142–143°, $[\alpha]_D$ −107°, λ_{max}^{MeOH} 239 mμ (ε 13,900).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.19; H, 8.60; O, 17.20. Found: C, 73.83; H, 8.55; O, 17.33.

20α-Hyroxypregn-4-en-3-one 6,19-Oxide (8a).—A solution of the 20-acetate **7a** (3.6 g) in methanol (175 ml) containing potassium hydroxide (5 g) was allowed to stand at room temperature for 2.5 hr. The mixture was then concentrated *in vacuo* at 50° and partitioned between methylene chloride and water. The usual work-up afforded the title compound **8a**, which crystallized from cyclohexane–methylene chloride (2.4 g), mp 146–151°. The analytical sample had mp 154–155°, $[\alpha]_D$ −110°, λ_{max}^{MeOH} 240 mμ (ε 13,500).

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.36; H, 9.09. Found: C, 76.26; H, 9.18.

20α-Hydroxypregn-4-en-3-on-18-oic Acid 6β,19-Oxide 20→18-Lactone (2a).—A solution of the 20-hydroxy compound **8a** (500 mg) in pyridine (15 ml) was treated with an excess of nitrosyl chloride. The solution was then poured into ice water and extracted with methylene chloride. The organic extract was washed exhaustively with water, filtered, and taken to dryness to afford the 20-nitrite **9a** as a crystalline solid. This compound was not further characterized but was processed immediately as below.

The crude nitrite **9a** was dissolved in dry toluene and irradiated (200-W lamp) at room temperature for 2 hr. The solvent was then removed and the crude product redissolved in acetic acid (68 ml) and water (12 ml). The solution was heated to 70° and treated with sodium nitrite (500 mg) for 2 min. Ice was then added and the mixture partitioned between half-saturated salt solution and methylene chloride. The organic phase was washed with saturated sodium bicarbonate, dried, and concentrated to dryness. The crude hemiacetal **11a** was then dissolved in acetone (80 ml) and treated with an excess of Jones reagent.[10] After 5 min, the excess oxidant was decomposed with methanol and the reaction mixture partitioned between methylene chloride and water. After the usual work-up, the product **2a** was obtained from methanol (176 mg), mp 230–285°. An analytical specimen had mp 282–288° (crystal change at 250°), $[\alpha]_D$ −129°, λ_{max}^{MeOH} 237.5 mμ (ε 14,900).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.68; H, 7.60. Found: C, 73.89; H, 7.75.

5α-Bromopregnane-3β,6β,20β-triol 3,20-Diacetate (4b).—A solution of 3β,20β-dihydroxypregn-5-ene 3,20-diacetate (**3b**, 1 g) in dioxane (12 ml) containing perchloric acid (0.5 ml as above) was treated with N-bromoacetamide (950 mg, added in four portions at 10-min intervals). The reaction mixture was stirred at room temperature for an additional 30 min and then worked up as above to afford the title compound **4b** which was crystallized

(11) F. Sondheimer and G. Rosenkranz, *Experientia*, **9**, 62 (1953).

(12) The reaction carried out in *t*-butyl alcohol was incomplete after 24 hr; compare with ref 13.

(13) S. H. Burstein and H. J. Ringold, *J. Amer. Chem. Soc.*, **86**, 4952 (1964).

(14) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Lett.*, No. 9, 14 (1960).

from cyclohexane–methylene chloride (570 mg): mp 162–165°; $[\alpha]D$ −23.1° (lit.[15] mp 163–164°; $[\alpha]D$ −23°).

5α-Bromopregnane-3β,20β-diol 6,19-Oxide 3,20-Diacetate (6b).—A stirred solution of the bromohydrin **4b** (1 g) in dry benzene (77 ml) containing iodine (1.2 g) and lead tetraacetate (2.5 g) was irradiated (200-W lamp) overnight at room temperature. After the usual work-up (*vide supra*), the title compound **6b** was obtained from methanol (500 mg): mp 169.5–171.5°, $[\alpha]D$ +20.8° (lit.[15] mp 164–165°, $[\alpha]D$ +21°).

Alternate Preparation of 6b.—A solution of the bromohydrin **4b** (1 g) in pyridine (25 ml) was treated with excess nitrosyl chloride at 0°. Ice was added to decompose excess nitrosyl chloride. On dilution of the reaction mixture with water the nitrite separated as a solid. It was collected, washed with water, dissolved in benzene (500 ml), and the solution dried over sodium sulfate. Iodine (0.24 g) and pyridine (0.1 ml) were added and the mixture was irradiated (500-W lamp) for 1 hr. The usual work-up (*vide supra*) afforded **6b** (375 mg) identical in all respects with the material described above.

5α-Bromopregnane-3β,20β-diol 6,19-Oxide 20-Acetate.—A solution of the diacetate **6b** (2.5 g) in ethanol–water (625 ml, 3:1) containing sodium hydroxide (1.9 g) was allowed to stand overnight at 5°. Acetic acid was then added and the mixture worked up as usual to afford the title compound crystallized from methanol (2.4 g). The analytical specimen had mp 60, 100, 191–195°; $[\alpha]D$ +16.3°.

Anal. Calcd for $C_{23}H_{35}O_4Br$: C, 60.66; H, 7.69; Br, 17.58. Found: C, 60.66; H, 7.63; Br, 17.67.

20β-Hydroxypregn-4-en-3-one 6β,19-Oxide 20-Acetate (7b).—A solution of the monoacetate from above (2.15 g) in acetone (150 ml) was treated with excess Jones reagent.[10] After 15 min, the excess oxidant was decomposed with methanol and the reaction mixture worked up as usual. The crude product was dissolved in methanol (250 ml) containing potassium acetate (12.5 g) and the solution heated under reflux for 0.5 hr. The usual work-up afforded the title compound **7b**, which was crystallized from methanol (1.1 g), mp 200–207°. The analytical specimen had mp 205–206°, $[\alpha]D$ −39°.

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.19; H, 8.60; O, 17.20. Found: C, 74.06; H, 8.76; O, 17.51.

20β-Hydroxypregn-4-en-3-one 6,19-Oxide (8b).—A solution of the monoacetate **7b** (1 g) in a mixture of methanol (15 ml), ethanol (15 ml), and tetrahydrofuran (10 ml) containing potassium hydroxide (1.5 g) was allowed to stand at room temperature overnight. The usual work-up afforded the title compound **8b**, which was recrystallized from cyclohexane–methylene chloride (720 mg), mp 202–211°. The analytical specimen had mp 207–211°, $[\alpha]D$ −116°.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.36; H, 9.09. Found: C, 76.23; H, 9.21.

20β-Hydroxypregn-4-en-3-on-18-oic Acid 6β,19-Oxide 20→18-Lactone (2b).—A solution of the alcohol from above (**8b**, 1 g) in pyridine (10 ml) was treated at 5° with an excess of nitrosyl chloride. The product crystallized on addition of water and was recrystallized from hexane to give the crude nitrite **9b** (0.8 g), mp 150–162°. The solution of this nitrite (0.75 g) in toluene (200 ml) was irradiated (200-W lamp) for 1 hr. The solvent was then removed *in vacuo* and the crude product chromatographed on alumina. Elution with 1% methanol in methylene chloride gave the crude oxime **10b**. The oxime was, without further purification, dissolved in acetic acid (5 ml) and the solution treated with sodium nitrite (200 mg) in water (2.5 ml). After 5 min, the reaction mixture was worked up as usual and the crude product redissolved in acetone (3 ml). The acetone solution was treated with an excess of Jones reagent.[10] After 5 min, the excess oxidant was decomposed with methanol and the reaction mixture worked up in the usual way to afford the title compound **2b** crystallized from ether (190 mg), mp 255–258°. The analytical specimen had mp 255–258°, $[\alpha]D$ −158°.

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.65; H, 7.65; O, 18.64. Found: C, 73.87; H, 7.59; O, 18.68.

19,20α-Dihydroxypregn-4-en-3-on-18-oic Acid 20→18-Lactone (12).—A solution of the oxidolactone **2a** (360 mg) in acetic acid (70 ml) was heated under reflux and treated with zinc dust (5 g, added in three portions at 5-min intervals). The zinc dust was removed by filtration and washed with methylene chloride. The combined organic portions were taken to dryness and partitioned between water and methylene chloride. The methylene chloride was then washed with sodium bicarbonate, dried, and concentrated *in vacuo*. The title compound **12** was obtained on crystallization from methanol (256 mg), mp 205–240°. An analytical sample had mp 243–248°, $[\alpha]D$ +85.2°, λ_{max} 242 mμ (ε 17,000).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.25; H, 8.14. Found: C, 73.01; H, 8.27.

20α-Hydroxypregn-4-en-3-on-18-oic Acid 6β,19-Oxide 20→18-Lactone 3-Ethylene Ketal (14).—A mixture of the oxidolactone **2a** (575 mg), *p*-toluenesulfonic acid (26 mg), and ethylene glycol (16 ml) was slowly distilled under vacuum (2 mm) until 8 ml of distillate had been collected. The reaction mixture was then cooled, treated with 7% aqueous sodium bicarbonate, and partitioned between methylene chloride and water. The organic phase was dried and evaporated. The residual solid was recrystallized from methanol to give the title compound **14** (350 mg), mp 198–215°. An analytical sample had mp 206–220°; $[\alpha]D$ −35.5°.

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.50; H, 7.77. Found: C, 71.41; H, 7.67.

18,19,20α-Trihydroxypregn-4-en-3-one 18,20-Diacetate.—A solution of the ketal **14** (620 mg) in tetrahydrofuran (10 ml) was added slowly to a stirred slurry of lithium aluminum hydride (700 mg) in tetrahydrofuran (20 ml). The mixture was heated under reflux for 0.5 hr after addition was complete. Water was then cautiously added and the product isolated with methylene chloride. The crude product was allowed to stand overnight in acetic anhydride (20 ml) and pyridine (25 ml). The mixture was then taken to dryness and the residue partitioned between methylene chloride and water. The methylene chloride was dried and concentrated to afford an oil (760 mg), which resisted attempts at crystallization.

A solution of the above crude material (760 mg) in acetone (40 ml) containing *p*-toluenesulfonic acid (40 mg) was allowed to stand at room temperature for 2 hr. The reaction mixture was then treated with aqueous sodium bicarbonate and concentrated to dryness. The crude product was partitioned between methylene chloride and water. The organic phase was removed, dried, and evaporated. The resultant oil, which resisted attempts at crystallization, was chromatographed on alumina (35 g). Elution with 2% acetone in methylene chloride afforded an oil (431 mg), the infrared spectrum of which revealed a band at 1660 cm^{-1} (α,β-unsaturated ketone). This crude material was dissolved in acetic acid (100 ml). The solution was heated under reflux and treated with zinc dust (7.0 g, added in six portions at 2.5-min intervals). After the usual work-up, the crude product was chromatographed on alumina (35 g). Elution with acetone and methylene chloride gave the title compound (260 mg). An analytical sample had mp 183–186°, $[\alpha]D$ +117°, λ_{max}^{MeOH} 242 mμ (ε 15,500).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.44; H, 8.33. Found: C, 69.60; H, 8.42.

18,19,20α-Trihydroxypregn-4-en-3-one (1a).—A solution of the 18,20-diacetate of the title compound (200 mg) in methanol (45 ml) containing potassium hydroxide (1 g) was allowed to stand at room temperature for 3 hr. The reaction mixture was then neutralized with dilute acetic acid, concentrated to small bulk, and partitioned between half-saturated salt solution and ethyl acetate. The organic portion was dried and evaporated to afford the crude product. An aliquot (85 mg) was then chromatographed on silica gel (15 g). Elution with 8–15% methanol in methylene chloride gave the title compound **1a** (64 mg), mp 235–250°. The analytical sample had mp 241–250°, $[\alpha]D$ +131°, λ_{max}^{MeOH} 243 mμ (ε 14,400).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.37; H, 9.25; O, 18.36. Found: C, 72.04; H, 9.52; O, 18.28.

18,20β,Dihydroxypregn-4-en-3-one 6,19-Oxide (18).—A solution of the oxidolactone **2b** (400 mg) in dry, freshly distilled tetrahydrofuran (25 cc) was treated with lithium aluminum hydride (400 mg). The suspension was heated under reflux for 2.5 hr and then worked up as usual. The crude mixture of triols was, without further purification, dissolved in *t*-butyl alcohol (30 cc) and treated with dichlorodicyanoquinone (310 mg). After storage for 24 hr at room temperature, the reaction mixture was worked up as usual[14] to afford the title compound **18** (210 mg). An analytical specimen had mp 99–100, 158–160, 175–176°; $[\alpha]D$ −162°; λ_{max}^{MeOH} 238 mμ (ε 12,700).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.79; H, 8.73; O, 18.47. Found: C, 73.14; H, 8.71; O, 17.99.

(15) J. Kalvoda, K. Heusler, H. Ueberwasser, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **46**, 1361 (1963).

18,19,20β-Trihydroxypregn-4-en-3-one (1b).—Zinc dust (75 g) and sufficient 3 *N* HCl to make a paste were heated on the steam bath for 30 min. The zinc was filtered off, washed with water and ethanol, and the resulting cake ground in a mortar under ethanol. The powdered zinc was then suspended in dilute acetic acid, filtered, and washed with water and acetic acid.

A solution of the 6,19-oxido compound (350 mg) in acetic acid (10 cc) was heated with vigorous agitation on the steam bath. Zinc, prepared as above, was then added (7 g, in portions over 13 min). The reaction mixture was cooled, filtered, and worked up as usual to afford the crude product, which was chromatographed on silica gel (30 g). Elution with 8–16% methanol in methylene chloride gave the title compound **1b** recrystallized from methylene chloride–ether (220 mg), mp 194–197°. An analytical sample had mp 198–204°, $[\alpha]D$ +78°, λ_{max}^{MeOH} 243 mμ (ε 14,000).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.37; H, 9.25; O, 18.36. Found: C, 72.32; H, 9.35; O, 18.22.

Registry No.—**1a**, 15833-26-8; **1b**, 15833-27-9; **2a**, 15833-28-0; **2b**, 15833-29-1; **4a**, 15833-30-4; **6a**, 15833-31-5; 5α-bromopregn-3β,20α-diol 6β,19-oxide 20-acetate, 15833-32-6; **7a**, 15833-33-7; **7b**, 15833-34-8; **8a**, 15833-35-9; **8b**, 15856-42-5; **12**, 15833-40-6; **14**, 15833-37-1; 18,19,20α-trihydroxypregn-4-en-3-one 18,20-diacetate, 15833-38-2; **18**, 15833-39-3.

A Rearrangement Reaction of 17-α-Hydroperoxypregnan-20-ones

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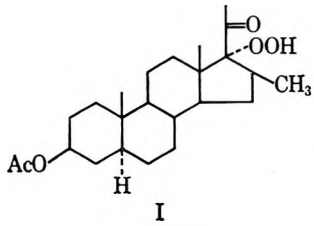
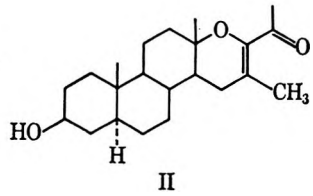
17α-Hydroperoxy-16β-methylpregnan-20-ones have been found to rearrange to 17a-oxa-D-homopregnan-20-ones upon acetylation or treatment with mineral acid. The structure, stereochemistry, and mode of formation of the products are discussed.

Although the preparation of 17α-hydroperoxypregnan-20-ones has been described,[2] their acylation has not been reported. While attempting the acetylation of 17α-hydroperoxy-16β-methyl-5α-pregnan-3β-ol-20-one 3-acetate (I) with a pyridine–acetic anhydride mixture, we were surprised to find that the crude product absorbed in the ultraviolet, having a band at λ_{max} 278 mμ.



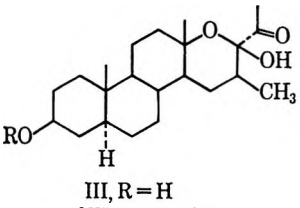
I



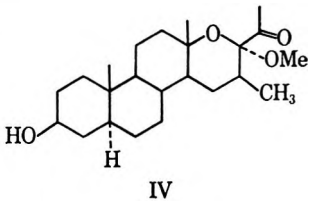
II

Chromatographic analysis revealed the presence of several materials and an investigation of their nature was undertaken.

Chromatography of the mixed acetates failed to resolve the mixture into its components and it was therefore subjected to hydrolysis with excess potassium hydroxide in aqueous methanol at room temperature. From the resulting mixture of alcohols three crystalline materials, II, III, and IV, were readily obtained by partition chromatography. Their structures were assigned on the basis of the following evidence.

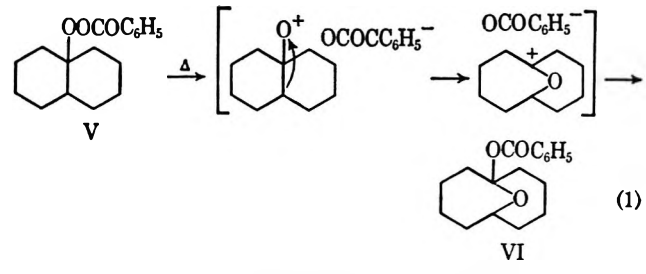


III, R = H
VII, R = $COCH_3$



IV

The major product (II), obtained in *ca.* 25% yield, had an ultraviolet absorption maximum at 278 mμ (ε 5900) and analyzed for $C_{22}H_{34}O_3$, whereas infrared maxima at 1700 and 1620 cm^{-1} indicated the presence of a conjugated carbonyl group. As the Criegee rearrangement of hydroperoxide esters is a well-documented reaction,[3] a typical example being the conversion of the decalin hydroperoxide benzoate V into the isomeric compound VI (eq 1), it was apparent early in the investigation that structure II was mechanistically



V

VI

(1)

logical and fitted much of the available evidence. Although no good model could be found for the chromophore in II, the observed absorption did not seem inconsistent with such a structure. The nmr spectrum of II (see Table I) was also in agreement with the pro-

TABLE I

NMR DATA[a]

Compd	Chemical shift: C-18 Me	C-19 Me	C-21 Me	17-OH	17-OMe	3-OAc	C-6 Me
II	1.02	0.77	2.14				
XVIII	1.06	0.98	2.22			2.04	1.64
III	1.25	0.77	2.20	4.15			
			0.77				
XIX	1.25	0.95	2.20	4.15		1.98	1.58
			0.77				
IV	1.08	0.75	2.13		3.22		
			1.04				
XV	1.25	0.77	2.13		3.12		
			0.90				

[a] Expressed in parts per million.

(1) Author to whom correspondence should be addressed at Hoffmann-La Roche, Inc., Nutley, N. J. 07110.

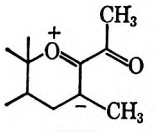
(2) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *J. Chem. Soc.*, 1578 (1962).

(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, N. Y., 1959, p 633.

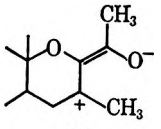
posed structure, with the exception that the resonance at 1.02 ppm which had to be ascribed to the C-18 methyl group was clearly too far upfield for methyl on carbon bearing oxygen. In addition, II did not undergo reactions typical of an enol ether or of an αβ-unsaturated ketone (for example, it was unaffected by mineral acid or zinc in acetic acid).

Attention was now directed to compound III, obtained in *ca.* 10% yield. This material did not absorb in the ultraviolet, analyzed for $C_{22}H_{36}O_4$, and had a single carbonyl absorption at 1730 cm^{-1}. On acetylation it yielded a monoacetate (VII) which had an infrared absorption at 3450 cm^{-1} showing that it still contained hydroxyl. These data were all consistent with structure III whose genesis *via* the Criegee rearrangement is obvious. The nmr spectrum was also in agreement. Notably the resonance at 1.25 ppm assigned to the C-18 methyl was in an acceptable position, and the only band in the spectrum which could not be unequivocally assigned was that at 4.15 ppm. This was tentatively ascribed to the proton of the hydroxyl group at 17, and it was shown that the band was absent from the spectrum after exchange with deuterium oxide. The stereochemistry at 17 remained unknown at this time.

The relationship of II to III was firmly established when it was discovered that III was converted into II on treatment with dilute mineral acid. This at once suggested that the anomalous position of the C-18 methyl resonance in the nmr spectrum of II was due to diamagnetic shielding by the 16 double bond. This conclusion was supported by an examination of models which revealed that the relative positions of the methyl group and the double bond were similar to those in other compounds where such shieldings have been reported.[4] In view of these developments it seemed reasonable to account for the lack of reactivity of the D ring in II as being due to contributions from canonical forms such as VIII and IX.

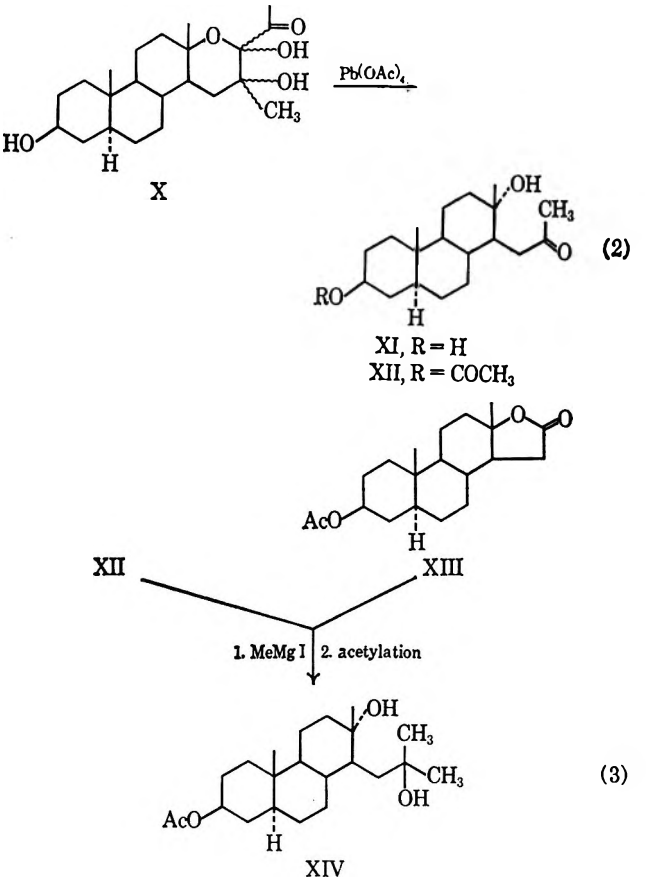


VIII



IX

As the structure of II seemed fairly secure on the basis of the evidence cited, degradation was undertaken. Reaction with osmium tetroxide yielded a mixture of glycols (X) which had spectral properties in accord with the proposed structure. In particular the C-18 methyl resonance occurred at 1.25 ppm and, as in III, there was a peak at 4.10 ppm assignable to the 17-hydroxyl. Reaction of X with lead tetraacetate, followed by alkaline hydrolysis, gave a methyl ketone (XI) which was converted into its 3-acetate (XII) with acetic anhydride in pyridine[5] (eq 2). An attempted iodoform degradation of XI to XIII was inconclusive, the lactone being formed in too small a yield to be obtained pure. An authentic sample of the lactone (XIII) was therefore prepared[6] and both it and XII were treated withe xcess methylmagnesium iodide followed by acetic anhydride–pyridine, affording thereby the same product, the triol acetate XIV (see eq 3). The structure of II is thus firmly established.



X

XI, R = H
XII, R = $COCH_3$

XII → XIII

1. MeMgI 2. acetylation

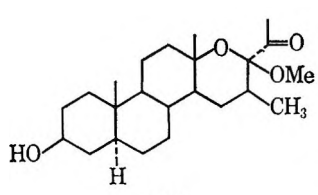
XIV

The third rearrangement product (IV), obtained from I in *ca.* 1% yield, was now examined. The compound analyzed for $C_{23}H_{38}O_4$, it had an infrared absorption band at 1725 cm^{-1}, and its nmr spectrum (see Table I) contained a band at 3.22 ppm ascribable to a methoxyl group. These data suggested that the compound might be a methyl ether of III, a hypothesis which was supported by its conversion into II on treatment with dilute mineral acid. An explanation of the formation of IV was then sought and it was thought that it might have been formed from III when the methanolic hydrolysis mixture of the crude rearrangement product was acidified with acetic acid. Compound III was therefore warmed with methanolic acetic acid and an isomeric ether (now assigned structure XV) was isolated. This material was identical with IV in chromatographic mobility, but whereas its infrared and nmr spectra showed similarities to those of IV, there were also profound differences. It was especially notable that in the nmr spectra (see Table I) of III and XV the C-18 methyl resonances occurred at 1.25 ppm whereas in IV this resonance was at 1.08 ppm. An examination of models of 17a-oxa-D-homopregnan-20-ones indicates that in a compound with a 17β-acetyl group the C-18 methyl should be diamagnetically shielded by the 20-ketone, whereas a 17α-acetyl group should have relatively little effect at C-18. As the C-18 methyl resonance in IV is shifted upfield relative

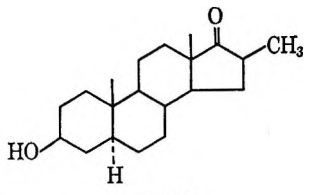
(4) R. R. Fraser, *Can. J. Chem.*, **40**, 78 (1962).

(5) The nmr absorption of the C-18 methyl group in XII is worthy of comment as it occurs at 1.00 ppm, the same position as in II. Examination of models reveals that if a hydrogen bond is formed between the 13α-hydroxyl and the 16-carbonyl, then the latter group is in a position to diamagnetically shield the C-18 methyl. Although the hydrogen bond postulated would form part of a seven-membered ring, the proposed explanation is supported by the fact that in XIV, where the carbonyl group is absent, the three methyl groups on carbon bearing oxygen lie in the range 1.12–1.25 ppm.

(6) S. Rakhit and M. Gut, *J. Org. Chem.*, **29**, 229 (1964).



XV



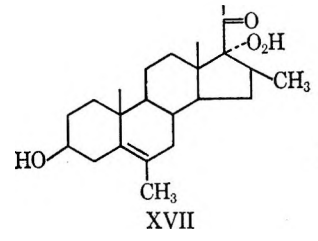
XVI

to the usual position for methyl on carbon bearing oxygen, IV was tentatively assigned the 17β-acetyl structure. If this is correct, III and XV should have the more stable 17α-acetyl configuration, in which the acetyl group is equatorial. These assignments were then confirmed by showing that IV yields XV in high yield on treatment with methanolic acetic acid.

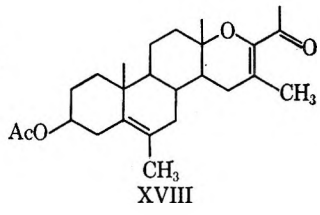
The aforegoing stereochemical arguments are supported by examination of the positions of the resonances due to the 16β-methyl group in the nmr spectra of III, IV, and XV. In IV the doublet ascribed to this group is centered at 0.99 ppm whereas in XV, evidently as the result of diamagnetic shielding by the 17α-acetyl group, this resonance is centered at 0.83 ppm. In III the doublet in question is observed at even higher field than in XV (0.71 ppm) an effect that is perhaps due to the influence of hydroxyl *vs.* methoxyl on the preferred rotational position of the 17α-acetyl group.

Before discussing the mechanism of the rearrangement, some further facts about the reaction and its products may be cited. It was found that if the acetylation of I was conducted with a limited amount of acetic anhydride and methanol was then added to the reaction mixture, the yield of IV could be raised to 22%. In contrast, if a large excess of anhydride was used, II was obtained in 62% yield and neither III nor IV could be isolated, while the best yield of II (*ca.* 80%) was obtained by acetylation of I with *p*-toluenesulfonic acid–isopropenyl acetate. Rearrangement of I could also be accomplished by treatment with perchloric acid in dioxane, and in this case II was isolated in 40% yield, together with a 14% yield of the 17-ketone XVI. It was also found that IV and XV yield III on treatment with trifluoroacetic acid in aqueous tetrahydrofuran, but prolonged exposure to these conditions can result in the formation of II.

When the hydroperoxide XVII was used as the substrate for the rearrangement, the reaction took the

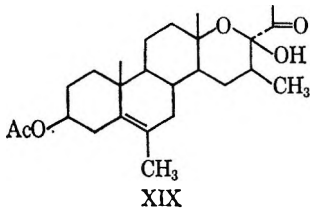


XVII



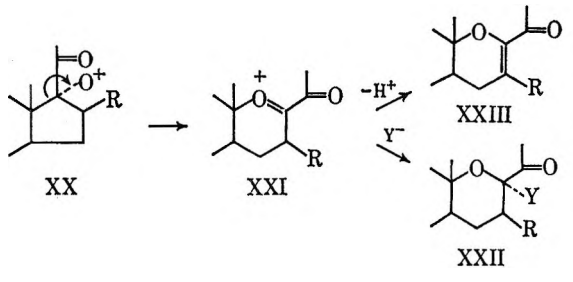
XVIII

expected course and XVIII and XIX were isolated. However, with 17α-hydroperoxy-5-pregnen-3β-ol-20-one the major product isolated was 5-androsten-3β-ol-17-one acetate, together with a small amount of 5-pregnene-3β,17α-diol-20-one 3-acetate. In this case the crude reaction product had an ultraviolet absorption maximum at 262 mμ, but we were unable to isolate the compound containing this chromophore as it appeared to decompose during chromatography. It was observed that variation of the amount of acetic anhydride used had no detectable effect on the course of this reaction.



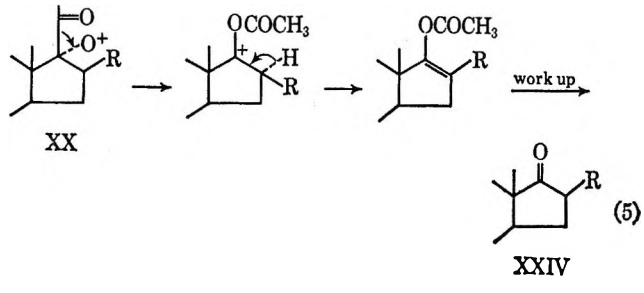
XIX

The D-homo products isolated from the rearrangements discussed are most easily rationalized in terms of a Criegee rearrangement[3] of the intermediate XX leading *via* XXI to XXII and XXIII (see eq 4). This



(4)

explanation defines neither the species which gives rise to XX nor the nature of Y in XXII. In addition, XX may undergo an alternative decomposition to yield the 17-ketone XXIV (eq 5), and the extent to which either



(5)

process predominates is evidently largely dependent on the nature of the substituent at 16. When a 16β-methyl group is present (XX, R = CH_3), the compression between this and the C-18 methyl group results in ring enlargement being the favored reaction. When the reaction is brought about with strong acid, XX presumably arises by protonation of the hydroperoxy function and subsequent loss of water. Likewise, it seems logical to assume that under acetylation conditions the acetate of the hydroperoxide forms and decomposes to XX. We have, however, been unable to detect the presence of this acetate. The formation of IV in *ca.* 20% yield, when methanol is added to an acetylation of I in which a limited amount of acetic anhydride is used, would appear to indicate that the reactive intermediate is present in appreciable amounts up to the time the methanol is added. Further, it is known that a steroidal 10β-hydroperoxyacetate has a carbonyl absorption at 1775 cm^{-1} in the infrared;[7] yet, examination of acetylations of I prior to quenching failed to detect any carbonyl absorption in this region. In addition, the thermodynamically unstable ether IV was originally isolated from a reaction mixture which had been quenched with water prior to coming into

(7) E. L. Shapiro, T. Legatt, and E. P. Oliveto, *Tetrahedron Lett.*, 663 (1964).

contact with methanol, suggesting that traces of the intermediate even survived water treatment. (That IV was not formed in this last experiment from II or III was established by showing that these compounds were stable in the presence of methanol and potassium hydroxide, and II was also shown to be stable in acidic methanol.) If XX does arise from the acetate of the hydroperoxide, then during the rearrangement of I, Y in XXII should be acetate prior to alkaline hydrolysis and epimerization to yield III. However, our inability to resolve the mixture of acetates prior to hydrolysis has left this point undetermined, and we have, therefore, no direct evidence for the formation of the acetate of the hydroperoxide, although its intermediacy does seem to offer a plausible explanation of the observed results.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope. Ultraviolet data refer to solutions in methanol, infrared data to Nujol mulls and rotations to approximately 1% solutions in dioxane. Nmr spectra were measured at 60-Mc for solutions in deuteriochloroform with tetramethylsilane as internal standard.

17α-Hydroxyperoxy-16β-methyl-5α-pregnan-3β-ol-20-one Acetate (I).—Sodium hydride (50% in oil; 3.75 g) was dissolved at room temperature in a mixture of *t*-butyl alcohol (50 ml) and dimethylformamide (75 ml). Dimethylformamide (125 ml) was added, the solution was cooled to −25° and a solution of 16β-methyl-5α-pregnan-3β-ol-20-one acetate (25 g) in tetrahydrofuran (60 ml) was added in one lot. A brisk stream of oxygen was blown through the solution while maintaining the temperature at −25°, and the reaction was monitored by thin layer chromatography using the system benzene–methanol (99:1). After 25 min when only a trace of starting material was detected, the solution was acidified with acetic acid. The product (28 g) was isolated by dilution with water and filtration. It was virtually homogeneous on thin layer chromatography. Two crystallizations from acetone–hexane gave an analytical sample: mp 170–173°; $[\alpha]_D$ +63.9°; ν_{max} 3300, 1750, 1700, and 1250 cm^{-1}.

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 71.12; H, 9.38.

Acetylation of 17α-Hydroperoxy-16β-methyl-5α-pregnan-3β-ol-20-one 3-Acetate. A. With Excess Acetic Anhydride.—The hydroperoxide (I) (1.22 g) in pyridine (7 ml) and acetic anhydride (3.5 ml) was left at room temperature for 18 hr. The mixture was poured into water and the crude product was isolated by extraction with ethyl acetate. The solvent was evaporated, and the residue hydrolyzed in a nitrogen atmosphere at room temperature for 1 hr with excess potassium hydroxide in aqueous methanol. The reaction mixture was acidified with acetic acid, and the product was precipitated by addition of water. After drying at 50°, this material was chromatographed on Chromosorb (100 g) in ligroin–propylene glycol, fractions of 30 ml being collected. Fractions 32–64 afforded 16-methyl-17a-oxa-D-homo-5α,16-pregnen-3β-ol-20-one (II) (649 mg). The analytical sample, crystallized from acetone–hexane, had mp 159–162°: $[\alpha]_D$ −79.5°; ν_{max} 1700 and 1620 cm^{-1}; λ_{max} 278 mμ (ε 5900). A second crystalline modification, mp 128–132°, was also obtained on some occasions.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.99; H, 9.96.

B. With a Limited Amount of Acetic Anhydride.—The preceding experiment was repeated with the quantity of acetic anhydride reduced to 610 mg.

Fractions 23–32 afforded 17α-methoxy-16β-methyl-17a-oxa-D-homo-5α-pregnan-3β-ol-20-one (IV) (112 mg) which crystallized from ether–hexane and had mp 128–135°. Several recrystallizations gave an analytical sample: mp 142–145°; $[\alpha]_D$ −30°; ν_{max} 3500 and 1725 cm^{-1}.

Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 72.54; H, 10.44.

Fractions 38–54 afforded II (333 mg).

Fractions 67–78 yielded 16β-methyl-17a-oxa-D-homo-5α,17-isopregnane-3β,17β-diol-20-one (III) (112 mg). This material crystallized from ether–hexane and had mp 173–178° with a change of crystal form in the range 130–150°. Two crystalline modifications with distinctly different infrared absorption spectra were encountered: $[\alpha]_D$ −42.5°; ν_{max} 1730 cm^{-1}.

Anal. Calcd for $C_{22}H_{36}O_4$: C, 76.26; H, 9.89. Found: C, 75.99; H, 9.96.

C. With a Limited Amount of Acetic Anhydride and Subsequent Addition of Methanol.—The hydroperoxide I (2.44 g) in pyridine (14 ml) and acetic anhydride (1.22 g) was left at room temperature for 18 hr. The reaction mixture under a nitrogen atmosphere, was diluted with excess potassium hydroxide in methanol and maintained at room temperature for 1 hr. Water was added and the product was isolated by extraction with ethyl acetate and chromatographed as in method A. Fractions 28–40 afforded IV (490 mg) and fractions 48–58 yielded II (625 mg).

16β-Methyl-17a-oxa-D-homo-5α,17-isopregnane-3β,17β-diol-20-one 3-Acetate (VII).—The diol III (110 mg) was acetylated in pyridine–acetic anhydride at room temperature for 18 hr. Water was added and the product was isolated by extraction with ethyl acetate and crystallized from aqueous ethanol to yield the 3-acetate (VII) (40 mg): mp 127–130°; $[\alpha]_D$ −46°.

Anal. Calcd for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.80; H, 9.43.

Treatment of III with Mineral Acid.—The diol III (50 mg) in methanol (2 ml) was treated with a few drops of 2 *N* hydrochloric acid and left at room temperature for 48 hr. The product was precipitated by addition of water and chromatographed in ligroin–propylene glycol on Chromosorb (25 g) to yield II (10 mg) identical with an authentic specimen as evidenced by mixture melting point and ultraviolet and infrared spectra.

16ζ-Methyl-17a-oxa-D-homo-5α-pregnane-3β,16ζ,17ζ-triol-20-one (X).—The olefin II (717 mg) in ether (30 ml) and pyridine (1 ml) was treated with a solution of osmium tetroxide (500 mg) in ether (15 ml). The mixture was stored in the dark for 3 days when the precipitate (1.25 g) was isolated by filtration and washed with ether. This material was dissolved in ethanol (125 ml) and 2% sodium metabisulfite solution (100 ml) was added. The reaction mixture was heated under reflux for 1.25 hr, filtered, and concentrated by boiling. It was then cooled and the product isolated by extraction with ethyl acetate. The resultant gum (shown by thin layer chromatography in chloroform–ethyl acetate 4:1 to be a mixture of two materials) was crystallized from aqueous ethanol to yield X (127 mg). Recrystallization from the same solvent gave an analytical sample: mp 166–177°; $[\alpha]_D$ −87°; ν_{max} 1700 cm^{-1}; nmr, 0.77 (C-19 methyl), 1.1 (16β-methyl), 1.24 (C-18 methyl), 2.26 (C-21 methyl), and 4.08 ppm (17-hydroxyl).

Anal. Calcd for $C_{22}H_{36}O_5 \cdot H_2O$: C, 66.30; H, 9.61. Found: C, 66.36; H, 9.78.

13,17-Seco-5α-androstane-3β,13α-diol-16-one (XI).—A solution of the triol (X) (981 mg) and lead tetraacetate (1.96 g) in chloroform (50 ml) was stirred at room temperature for 3.5 hr. The chloroform solution was washed with aqueous ethylene glycol and with water, and then dried over sodium sulfate. Evaporation of the solvent gave an oil which was treated with excess potassium hydroxide in aqueous methanol at room temperature for 1.5 hr. The reaction mixture was poured into dilute aqueous acetic acid and the product was isolated by extraction with dichloromethane. This material was chromatographed in toluene–propylene glycol on Chromosorb (50 g) and crystallized from acetone–hexane to yield XI (144 mg), mp 187–200°. A further crystallization gave an analytical sample: mp 190–204°; $[\alpha]_D$ −7.9°; ν_{max} 1700 cm^{-1}.

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 74.00; H, 10.09.

13,17-Seco-5α-androstane-3β,13α-diol-16-one 3-Acetate (XII).—The diol (XI) (80 mg) was acetylated in a pyridine–acetic anhydride mixture at room temperature for 18 hr to yield 34 mg of the 3-acetate (XII): mp 151–154° after two crystallizations from acetone–hexane; $[\alpha]_D$ −26°; ν_{max} 3500, 1710, and 1270 cm^{-1}; nmr, 0.73 (C-19 methyl), 1.00 (C-18 methyl), 1.94 (3β-acetate), and 2.10 ppm (C-16 methyl).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.75. Found: C, 71.92; H, 9.72.

16-Methyl-13,17-seco-5α-androstane-3β,13α,16-triol 3-Acetate (XIV) from XII.—The ketone XII (250 mg) in tetrahydrofuran (50 ml) was added to an excess of methylmagnesiumi odide in ether. The mixture was stirred 2.5 hr at room temperature, then poured into aqueous ammonium chloride solution. The product was isolated by filtration, dried, and acetylated in a

pyridine–acetic anhydride mixture at room temperature for 18 hr to yield XIV, mp 190–194° after two crystallizations from acetone–hexane: $[\alpha]D$ −32°; ν_{max} 1750 cm^{-1}; nmr, 0.77 (C-19 methyl), 1.12, 1.17, 1.25 (C-18 methyl and 16,16-dimethyl), and 2.00 ppm (3β-acetate).

Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45. Found: C, 71.97; H, 10.66.

From 17-oxa-5α-androstan-3β-ol-16-one Acetate (XIII).—The lactone (XIII)[6] (60 mg) in tetrahydrofuran (10 ml) was added to an excess of methylmagnesium iodide in ether. The product was isolated, acetylated, and crystallized as described above to yield XIV (8 mg), mp 188–192°, identical with the product obtained from XII as evidenced by mixture melting point and infrared absorption.

Treatment of IV with Mineral Acid.—The methyl ether IV (63 mg) in tetrahydrofuran (8 ml) was treated with a few drops of 2 *N* hydrochloric acid, and the solution was warmed on the steam bath for 1 hr. The product was precipitated by addition of water and crystallized from acetone–hexane to yield II (29 mg) identical with an authentic specimen.

17β-Methoxy-16β-methyl-17a-oxa-D-homo-5α,17-isopregnan-3β-ol-20-one (XV). A. From IV.—A solution of IV (88 mg) in methanol (6 ml) containing a few drops of acetic acid was warmed on the steam bath for 3 hr. Addition of water and crystallization of the resultant precipitate from acetone–hexane gave XV (45 mg): mp 180–192°; $[\alpha]D$ −110°; ν_{max} 3550, 3450, 1750, and 1730 cm^{-1}.

Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 73.05; H, 10.28.

B. From III.—A solution of III (110 mg) in methanol (5 ml) containing a few drops of acetic acid was warmed on the steam bath for 3 hr. Water was added, and the product was isolated by extraction with ethyl acetate and chromatographed in ligroin–propylene glycol on Chromosorb (36 g), fractions of 15 ml being collected. The material in fractions 12–18 was crystallized from acetone–hexane to yield XV (18 mg), mp 178–188°.

Rearrangement of I with Perchloric Acid.—The hydroperoxide I (3 g) suspended in dioxane (80 ml) and perchloric acid (70%; 8 ml) was stirred at room temperature for 18 hr. The product was precipitated with water and hydrolyzed and chromatographed as described for the rearrangement using acetic anhydride–pyridine. In addition to II (1.02 g), there was isolated from subsequent chromatogram fractions XVI (307 mg), mp 153–156° after crystallization from acetone–hexane. This material was identical with an authentic sample of 16β-methyl-5α-androstan-3β-ol-17-one.[8]

Rearrangement of I with Isopropenyl Acetate *p*-Toluenesulfonic Acid.—The hydroperoxide I (5.2 g) suspended in acetic acid (150 ml) and isopropenyl acetate (20 ml) was stirred at room temperature for 18 hr with *p*-toluenesulfonic acid (520 mg). The crude product was isolated by dilution with water and extraction with ethyl acetate. It was hydrolyzed and chromatographed as described for the rearrangement using acetic anhydride–pyridine to yield II (4.05 g).

Treatment of IV with Aqueous Trifluoroacetic Acid.—The methyl ether IV (1.06 g) in tetrahydrofuran (45 ml) and water (5 ml) was treated with trifluoroacetic acid (1 ml) and left at room temperature for 60 hr. The reaction mixture was poured into water, and the precipitate was isolated and crystallized from ether–hexane to yield III (630 mg), mp 168–173°.

6,16-Dimethyl-17a-oxa-D-homo-5,16-pregnadiene-3β-ol-20-one 3-Acetate (XVIII).—6,16β-Dimethyl-17α-hydroperoxy-5-pregnen-3β-ol-20-one[9] (3.1 g) was acetylated in a pyridine–acetic anhydride mixture for 18 hr at room temperature. The mixture of acetates was crystallized twice from aqueous methanol to yield XVIII (1.03 g), mp 175–178°. Four further crystallizations from methanol gave an analytical sample with mp 180–183°; $[\alpha]D$ −169°; λ_{max} 278 mμ; (ε 6200); ν_{max} 1740, 1700, 1630, and 1250 cm^{-1}.

Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.90; H, 9.17.

6,16β-Dimethyl-17a-oxa-D-homo-17-iso-5-pregnene-3β,17β-diol-20-one 3-Acetate (XIX).—The mother liquors from the first two crystallizations of XVIII were hydrolyzed with excess potassium hydroxide in aqueous methanol at room temperature. The crude product was chromatographed in ligroin–propylene glycol on Chromosorb (140 g), fractions of 50-ml volume being collected. The gum in fractions 53–72 (481 mg) was acetylated in the usual manner, and the product was crystallized from aqueous ethanol to yield XIX: mp 149–153°; ν_{max} 3450, 1720, and 1250 cm^{-1}.

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.39; H, 8.78.

Rearrangement of 17α-Hydroperoxy-5-pregnen-3β-ol-20-one.[2]—The hydroperoxide (1 g) was acetylated in a pyridine–acetic anhydride mixture at room temperature for 18 hr. The crude product, which had a band at λ_{max} 262 mμ (ε 500–1000), was chromatographed on Chromosorb (130 g) in heptane–methyl Cellosolve, fractions of 25 ml being collected.

Fractions 25–39.—This material (800 mg), which on paper chromatography in heptane–methyl Cellosolve appeared to be homogeneous and to absorb in the ultraviolet, was hydrolyzed in aqueous methanol at room temperature with excess potassium hydroxide. The product was chromatographed on Chromosorb (75 g) in ligroin–propylene glycol. The material in fractions 19–33, which likewise appeared to be homogeneous and to absorb in the ultraviolet, was crystallized from hexane–ether and then from aqueous methanol to yield 5-androsten-3β-ol-17-one (155 mg) identical with an authentic specimen. (Subsequent attempts to isolate the compound containing the chromophore failed due to its apparent decomposition.)

Fractions 40–60.—This material (275 mg) was hydrolyzed in aqueous methanol at room temperature with excess potassium hydroxide. The product was crystallized from methanol to give 5-pregnene-3β,17α-diol-20-one (70 mg) identical with an authentic specimen.

Registry No.—I, 15815-49-3; II, 15815-51-7; III, 15815-50-6; IV, 15811-05-9; VII, 15811-04-8; X, 15811-06-0; XI, 15811-07-1; XII, 15811-08-2; XIV, 15811-09-3; XV, 15811-10-6; XVIII, 15811-11-7; XIX, 15811-12-8.

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Flavonoids of Citrus. IX. Some New C-Glycosylflavones and a Nuclear Magnetic Resonance Method for Differentiating 6- and 8-C-Glycosyl Isomers

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6-C-β-D-Glucopyranosyldiosmetin and 8-C-β-D-glucopyranosyldiosmetin have been isolated from citrus species and their structures determined from nmr and other spectral data. In addition, 2''-O-β-D-xylosylvitexin, a di-C-glycosylapigenin, and a di-C-glycosyldiosmetin have been obtained. The chemical shifts of acetyl methyl bands in the nmr spectra of various acetylated C-glycosyl compounds are discussed. It is shown that these shifts as well as other spectral and chromatographic data can be used to determine the position of substitution of the glucosyl residue.

C-Glycosylflavones have been found in about twenty different plant families.[2,3] Earlier publications[4-6] dealt briefly with the occurrence of these compounds in citrus fruits (Rutaceae), where they accompany a large array of other flavonoids, principally O-glycosides and O-permethylflavones. For the most part the C-glycosylflavones of *Citrus* occur in very low concentration and are difficult to isolate. We obtained the compounds described here by chromatographing crude peel extracts on columns of silicic acid developed with chloroform–methanol or ethyl acetate–methanol.

Compound I, mp 267–268°, was found both in lemons (*C. limon*) and oranges (*C. sinensis*). Its ultraviolet spectra in neutral ethanol and with various added diagnostic reagents (Table I) establish it as a flavone. Comparison of these spectra with those of some commonly occurring flavone aglycones (see Chart I and Table I) indicates that it is derived from diosmetin. Since I moves faster than diosmetin on paper chromatography in aqueous solvents or on paper electrophoresis in aqueous sodium borate (Table II), it can be assumed that a glycosyl residue is present in the molecule. Nevertheless, prolonged treatment of the compound in hot 3 *N* hydrochloric acid fails to release any sugar, but leads instead to a slow, partial conversion into a different glycosylflavone (II).

Compound II, mp 243–245°, is a natural constituent of lemons, but was not found in oranges. Its ultraviolet spectra are almost indistinguishable from those of diosmetin and I. It migrates faster than I on paper chromatography or electrophoresis and, when heated in acid, undergoes partial conversion into I. Both I and II yield isovanillic acid as a product of alkaline hydrolysis.

It is clear that we have in hand a pair of isomeric C-glycosylflavones, one of which is a 6-C-glycosyl derivative, the other an 8-C-glycosyl derivative. This conclusion is based (a) on the obvious presence of a glycosyl residue, (b) on its failure to be released by acid hydrolysis, and (c) on the interconversion of I and II in acid solution. Analogous Wessley–Moser interconversions of 6- and 8-C-glycosyl isomers have been observed before, for example, in vitexin and isovitexin[4] or orientin and isoorientin.[7]

The remaining structural questions have to do with the identification, configuration, and point of attachment of the glycosyl residue. Because of the very small amount of material on hand, it was impractical to ozonize or otherwise oxidize the flavone portion of the molecule to obtain the free sugar. However, in cases where the identity of the sugar residue of C-glycosyl compounds has been clearly established, it has always been found to be β-D-glucosyl. That this holds for compounds I and II is indicated by nmr data, which also show the configuration and point of attachment of the glucosyl residue.

Table III catalogs the band positions of the aliphatic acetyl methyl groups of various acetylated 8- and 6-C-glucosylflavones (groups A and B, respectively) and of a number of miscellaneous acetylated C-glucosyl compounds (group C). The acetyl bands of the 8-substituted flavones form a pattern quite distinct from that of the acetyl bands of the 6-substituted and miscellaneous group. Thus, in 8-C-glucosylflavones both the 2''-O-acetyl band (δ 1.70–1.73) and the 6''-O-acetyl band (δ 1.90–1.95) occur at consistently higher field than they do in the other groups of compounds (δ 1.77–1.83 for the 2''-O-acetyl in groups B and C and 1.98–2.04 for the 6''-O-acetyl in groups B and C). There is, in fact, essentially no difference in the spectra of the group B and C compounds in spite of wide variations in structure. The distinct character of the spectra of the group A compounds must be due to some special structural feature, most likely the proximity of the glucosyl residue to the B ring of the flavone.

The unusually high field position of the 2''-O-acetyl band in the various compounds listed in Table III is due primarily to shielding by the aromatic A ring to which the glycosyl residue is linked, since this acetyl is situated mainly in the diamagnetic region above or below the plane of the A ring[5,8,9] (see Figure 1). The slightly greater shielding of the 2''-O-acetyl in group A compounds compared with group B and C compounds is of some diagnostic value and can be explained on the assumption that the 2''-O-acetyl in group A is shielded not only by the A ring of the flavone but to some extent by the B ring. The greater shielding of the 6''-O-acetyl in group A can be accounted for on the assumption that it lies in the diamagnetic region

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TABLE I

ULTRAVIOLET ABSORPTION SPECTRA (λ_{max} IN mμ) OF FLAVONES, *C*-GLYCOSYLFLAVONES, AND THEIR ACETYL DERIVATIVES[a]

Compd	In EtOH[b]	In EtOH–NaOAc[c]	In EtOH–NaOH[d]	In EtOH–AlCl₃[e]
I	252, 272, ~290, 343	281, ~320, ~370	270, ~303, ~385	259, 280, ~296, 355, ~380
I heptaacetate (Ia)	~260, 319			
II	253, 272, 344	280, ~318, ~376	271, ~302, ~390	259, 281, ~295, 358, ~380
II heptaacetate (IIa)	~258, 320			
III	272, 333	281, 384	281, ~334, 400	279, 306, 349, ~382
IV	274, 335	283, 385	283, ~337, 404	282, 305, 350, ~380
IV peracetate (IVa)	258, 298, ~312			
V	~257, 274, 344	283, ~315, ~385	269, ~280, ~400	~265, 282, ~300, 357, ~380
V peracetate (Va)	~257, 314			
Apigenin (VI)	269, 335	277, ~300, 380	277, ~329, 399	278, 303, 345, ~382
Apigenin triacetate (VIa)	254, 299			
Luteolin (VII)	255, 268, ~295, 350	269, ~277, ~325, 392	267, ~335, 406	273, ~300, ~332, 426
Luteolin tetraacetate (VIIa)	~254, 259, 298			
Chrysoeriol (VIII)	252, 270, 346	278, ~321, 395	265, 335, 410	263, 278, ~296, 359, ~385
Chrysoeriol triacetate (VIIIa)	240, ~260, 308			
Diosmetin (IX)	252, 269, 344	278, ~321, ~362	271, ~302, ~382	261, 278, ~295, 358, ~383
Diosmetin triacetate (IXa)	~255, 318			
Vitexin (X)	270, 333	280, ~300, 384	281, ~333, 400	278, 305, 346, ~382
Vitexin heptaacetate (Xa)	254, 398, ~310			
Isovitexin (XI)	273, 336	280, ~300, 383	280, ~333, 404	281, 305, 349, ~380
2″-*O*-β-D-Xylosylvitexin (XII)	271, 332	280, ~305, 386	281, ~333, 400	278, 305, 346, ~380

[a] The symbol ~ indicates either a shoulder or band of relatively low intensity. [b] Absolute ethanol. [c] Fused sodium acetate. [d] One drop of 1% aqueous sodium hydroxide added to a 3-ml cuvette. [e] Excess crystalline aluminum chloride.

TABLE II

MIGRATION OF FLAVONES AND *C*-GLYCOSYLFLAVONES ON PAPER CHROMATOGRAPHY AND ELECTROPHORESIS

	R_f value in				
Compd	10% HOAc	30% HOAc	*n*-BuOH–HOAc–H₂O (20:6:15)	EtOAc–HCO₂H–H₂O (10:2:3)[a]	Electrophoretic migration[b]
I	0.13	0.42	0.58	0.39	0.48
II	0.30	0.61	0.68	0.47	0.75
III	0.65	0.74	0.62	0.39	1.86
IV	0.50	0.68	0.55	0.15	1.80
V	0.39	0.64	0.52	0.13	1.35
Apigenin (VI)	0.03	0.28	0.94	0.87	0.30
Diosmetin (IX)	0.02	0.23	0.90	0.86	0.08
Vitexin (X)	0.20	0.46	0.63	0.43	1.00
Isovitexin (XI)	0.39	0.63	0.72	0.51	1.31
2″-*O*-β-D-xylosylvitexin (XII)	0.65	0.74	0.62	0.39	1.88
Vicenin-2 (XIII)	0.47	0.65	0.55	0.18	1.80
Orientin (XIV)	0.12	0.38	0.42	0.28	1.15
Isoorientin (XV)	0.27	0.56	0.55	0.38	1.50

[a] Upper phase. [b] In 0.1 *M* aqueous sodium borate, *ca.* 900 V, 20–40 mA, *ca.* 3 hr, Whatman No. 1 paper. The migrations are given relative to vitexin = 1.00.

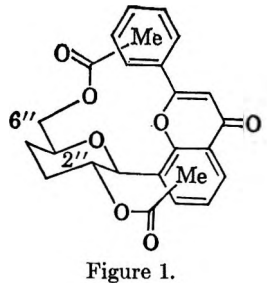


Figure 1.

of the B ring of the flavone nucleus. Models show this to be a likely conformation (see Figure 1). Since any similar shielding can obviously be ruled out in groups B and C, the 6″-*O*-acetyl band of these compounds occurs at the "normal" position (δ 1.98–2.04), *i.e.*, the same position as the 6-*O*-acetyl band of simple glucose derivatives such as D-glucose 2,3,4,6-tetraacetate (δ 2.03).[10]

A consequence of the interaction of the 2″- and 6″-*O*-acetyl groups with the B ring and C-7 substituent in 8-substituted flavones is that these compounds exhibit hindered rotation about the C-1″–C-8 bond. Even at temperatures as high as 30–40° they appear to exist largely in two principal rotational conformations,[11] as discussed earlier by Eade and coworkers.[9] The existence of the conformers, which is markedly temperature dependent, is evidenced in the nmr spectrum at 35° by the splitting or broadening of the bands of certain aromatic protons and acetyl groups, particularly the 6″-*O*-acetyl group (Table III). Since the glycosyl portion of the group B and C compounds has a smaller rotational barrier, their spectra are generally sharp in all regions, with the possible exception of the slightly broadened 2″-*O*-acetyl band.

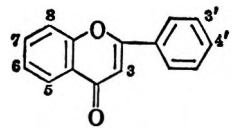
A further point of difference between the spectra of the acetylated 8-*C*-glucosylflavones and the other acetylated *C*-glucosyl compounds lies in the band posi-

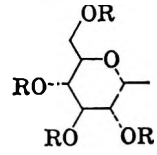
(10) The assignments in Table III for the acetyl bands of D-glucose 2,3,4,6-tetraacetate are based on a comparison of the spectra of various partially acetylated glucoses (unpublished data).

(11) One of these is the conformation shown in Figure 1; in the other the glucosyl residue is rotated 180° about the C-1″–C-8 bond.

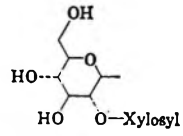
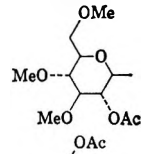
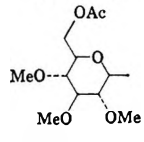
CHART I

FLAVONE SUBSTITUTION PATTERNS





Glu, R = H
Ac_4Glu, R = Ac

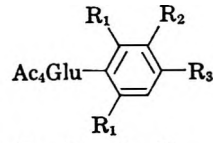
Compd	3	5	6	7	8	3′	4′
III, XII	...	OH	...	OH		...	OH
IV, XIII	...	OH	Glycosyl	OH	Glycosyl	...	OH
IVa	...	OAc	Peracetylglycosyl	OAc	Peracetylglycosyl	...	OAc
V	...	OH	Glycosyl	OH	Glycosyl	OH	OMe
Va	...	OAc	Peracetylglycosyl	OAc	Peracetylglycosyl	OAc	OMe
VI	...	OH	...	OH	...	...	OH
VIa	...	OAc	...	OAc	...	...	OAc
VII	...	OH	...	OH	...	OH	OH
VIIa	...	OAc	...	OAc	...	OAc	OAc
VIII	...	OH	...	OH	...	OMe	OH
VIIIa	...	OAc	...	OAc	...	OMe	OAc
IX	...	OH	...	OH	...	OH	OMe
IXa	...	OAc	...	OAc	...	OAc	OMe
X	...	OH	...	OH	Glu	...	OH
Xa	...	OAc	...	OAc	Ac_4Glu	...	OAc
XI	...	OH	Glu	OH	...	...	OH
XIa	...	OAc	Ac_4Glu	OAc	...	...	OAc
XIV	...	OH	...	OH	Glu	OH	OH
XIVa	...	OAc	...	OAc	Ac_4Glu	OAc	OAc
XV	...	OH	Glu	OH	...	OH	OH
XVa	...	OAc	Ac_4Glu	OAc	...	OAc	OAc
XVIa	...	OAc	...	OAc	Ac_4Glu	...	OMe
XVIIa	...	OMe	...	OMe	Ac_4Glu	...	OMe
XVIIIa	...	OMe	...	OMe		...	OMe
XIXa	...	OMe	...	OMe		...	OMe
XXa	...	...	...	OAc	Ac_4Glu	...	OAc
XXIa	...	...	...	OMe	Ac_4Glu	...	OMe
XXIIa	...	OMe	Ac_4Glu	OMe	...	...	OMe
XXIIIa	OAc	OAc	Ac_4Glu	OMe	...	...	OAc
XXXIIa	...	OAc	...	OAc	...	...	OMe

tions of the 3″- and 4″-*O*-acetyl groups. In the 8-substituted flavones these bands occur in two discrete ranges, δ 2.01–2.03 and 2.08–2.10, respectively, while in the 6-substituted and miscellaneous compounds they overlap or occur very close together in the range δ 2.03–2.08. Since the 4″-*O*-acetyl lies near the axis of rotation of the glucosyl ring, it should be relatively insensitive to the rotational conformation of the molecule. In the 8-substituted flavones the signal at δ 2.08–2.10 is a sharp singlet and is, therefore, assigned to the 4″-*O*-acetyl. The band at δ 2.01–2.03 is usually broadened or split and is assigned to the 3″-*O*-acetyl. Furthermore, models show that in one of the principal postulated conformations the 3″-*O*-acetyl is likely to be shielded to some extent by the B ring.[12,13]

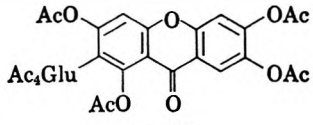
Using the band positions of the various sugar acetyl groups and sharpness of the spectra as criteria for determining the point of substitution, we conclude

(12) The same assignments for the 3″- and 4″-*O*-acetyls have been given by Eade, Hillis, Horn, and Simes[9] but the converse assignments are given by Hillis and Horn.[8]

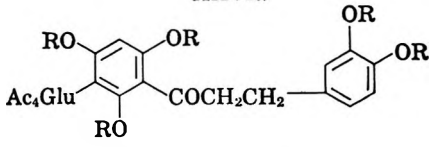
(13) The spectrum of the isoflavone, puerarin hexaacetate (XXXIa), appears to be of a "hybrid" nature, in which the 2″-*O*-acetyl signal conforms to the group A pattern while the 3″-, 4″-, and 6″-*O*-acetyl signals conform to the group B, C pattern. Models show that the 2″-*O*-acetyl group is roughly equidistant from the B ring in 8-substituted flavones or isoflavones, but the other acetyl groups are much further removed from the B ring in 8-substituted isoflavones than in 8-substituted flavones. It is also of interest that the 6- and 8-substituted flavanones, hemiphloin heptaacetate (XXXa) and isohemiphloin heptaacetate (XXIXa), are reported to give closely similar spectra.



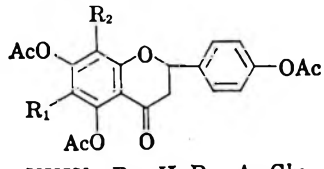
XXIVa, $R_1=R_2=R_3=H$
XXVa, $R_1=OMe$; $R_2=Ac$; $R_3=OAc$



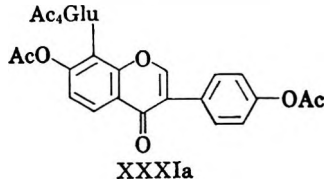
XXVIa



XXVIIa, R = Ac
XXVIIIa, R = Me



XXIXa, $R_1=H$; $R_2=Ac_4Glu$
XXXa, $R_1=Ac_4Glu$; $R_2=H$

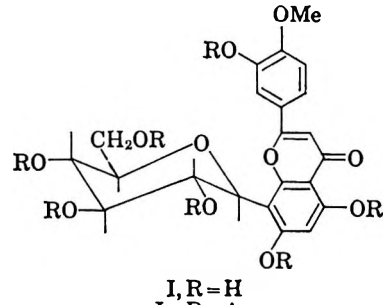


XXXIa

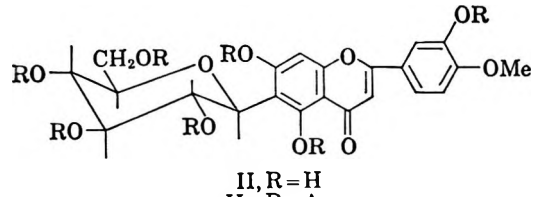
that compound I is an 8-substituted diosmetin and compound II is a 6-substituted diosmetin. The close correspondence in the acetyl band positions of Ia and IIa with those of the other compounds in their respective groups, all of which are *C*-β-D-glucosyl derivatives, leads us to infer that they too are *C*-β-D-glucosyl derivatives. Were this not the case one might expect to find perceptible differences in the spectra as a result of epimeric configurations in the sugar. In any case, the large coupling constant (10 Hz) of H-1″ in compound IIa (Table III) confirms the β configuration of the glucosyl radical and the equatorial configuration of the C-2″ acetoxyl group.

The nmr data in Table IV show the band positions of the aromatic and methoxyl protons in the acetyl derivatives of II, vitexin, isovitexin, and several simple flavones. The latter compounds—apigenin, acacetin, luteolin, chrysoeriol and diosmetin—give characteristic spectra that are useful in identifying *C*-glucosyl compounds derived from them. Comparison of the chemical shifts in Table IV shows, in agreement with the ultraviolet data of Table I, that compound II is derived from diosmetin, while the absence of an H-6 resonance confirms that it is 6 substituted.[14]

The problem of distinguishing 6- and 8-*C*-glucosyl isomers can be solved, as outlined above, by examining the chemical shifts of either the acetyl or aromatic protons. When only a small amount of compound is available the acetyl protons, because of greater signal strength, generally give more reliable information than do the aromatic protons, which sometimes cannot be discerned above the background. Confirmatory evidence can be obtained by comparing R_f values of the corresponding 6- and 8-*C*-glucosylflavones. In the solvents listed in Table II the 6-substituted compounds invariably migrate more rapidly than the corresponding 8-substituted compounds, and the same applies for paper electrophoresis in sodium borate solution.[15-17] According to these criteria compounds I and II can again be assigned as the 8 and 6 isomers, respectively. We conclude that I is 8-*C*-β-D-glucopyranosyldiosmetin and II is 6-*C*-β-D-glucopyranosyldiosmetin.



I, R = H
Ia, R = Ac



II, R = H
IIa, R = Ac

In addition to these monoglucosylflavones we have isolated small quantities of flavones that appear to contain more than one glycosyl residue. Compound III, obtained as a gum from orange peel, yields xylose and vitexin together with a small amount of isovitexin when hydrolyzed with acid or hemicellulase. Its ultraviolet spectra (Table I) are the same as those of 2″-*O*-β-D-xylosylvitexin,[5] as are its R_f values in several solvents and rate of migration on paper electrophoresis (Table II). 2″-*O*-β-D-Xylosylvitexin was isolated previously from *Vitex lucens* as a crystalline solid. The present compound, which was not obtained entirely pure, is believed to consist mainly of 2″-*O*-β-D-xylosylvitexin mixed with a small proportion of a glycosylisovitexin.

Compound IV was isolated from lemon peel as a crystalline solid, mp 233–236°. Its ultraviolet spectrum and spectral shifts are closely similar to those of apigenin, vitexin, and isovitexin. It migrates more rapidly than any of these compounds on paper chromatography in strongly aqueous solvents or on paper electrophoresis in aqueous sodium borate. When heated in hydrochloric acid it gives no sugar and does not isomerize appreciably. These results point to the presence of two *C*-glycosyl residues, which, because of the apparent lack of isomerization, are likely to be identical and located at the 6 and 8 positions of the

(14) There was an insufficient quantity of Ia available to determine reliable values for the aromatic protons. The methoxyl protons in Ia occur at δ 3.93.

(15) Other examples, not given in Table II, are cytisoside/isocytisoside[1,16] and swertisin/isoswertisin.[17]

(16) J. Chopin, M. L. Bouillant, and A. Durix, *Compt. Rend.*, **260**, 4850 (1965).

(17) M. Komatsu, T. Tomimori, and M. Ito, *Chem. Pharm. Bull.* (Tokyo), **15**, 263 (1967); M. Komatsu and T. Tomimori, *Tetrahedron Lett.*, 1611 (1966).

TABLE III
CHEMICAL SHIFT OF ACETYL METHYL AND BENZYLIC (H-1'') PROTONS OF ACETYLATED C-GLUCOSYL COMPOUNDS IN DEUTERIOCHLOROFORM[a]

Compd	Chemical shift and coupling [δ, ppm (J, Hz)] 4''-OAc	3''-OAc	6''-OAc	2''-OAc	H-1''	Ref[b]
8-Substituted Flavones (Group A)						
Vitexin heptaacetate (Xa)	2.09	2.01	1.91[c]	1.73	4.98 (10)	5
Cytisoside hexaacetate (XVIa)	2.08	2.01	1.92	1.73	*d*	16
5,7,4'-Tri-*O*-methylvitexin tetraacetate (XVIIa)	2.09	1.98	1.93[c]	1.71	5.25 (10)	
5,7,4',3'',4'',6''-Hexa-*O*-methylvitexin acetate (XVIIIa)	...	...	...	1.72	5.06 (10)	5
5,7,4',2'',3'',4''-Hexa-*O*-methylvitexin acetate (XIXa)	...	...	1.93	...	5.00 (10)	5
Orientin octaacetate (XIVa)	2.09	2.02	1.95[e]	1.72	*b*	
Bayin hexaacetate (XXa)	2.10	2.02[g]	1.90[h]	1.72	*d*	8, 9
7,4'-Di-*O*-methylbayin tetraacetate (XXIa)	2.10	2.01[g]	1.91[h]	1.70	*d*	8, 9
8-*C*-β-D-Glucopyranosyldiosmetin heptaacetate (Ia)	2.08	2.02	1.94[e]	1.71	*f*	
Range for group A	(2.08–2.10)	(1.98–2.02)	(1.90–1.95)	(1.70–1.73)		
6-Substituted Flavones (Group B)						
Isovitexin heptaacetate (XIa)	2.08	2.08	2.04	1.83	4.91 (10)	
5,7,4'-Tri-*O*-methylisovitexin tetraacetate (XXIIa)	2.07	2.05	2.02	1.77	5.14 (10)	
Isoorientin octaacetate (XVa)	2.08	2.08	2.02	1.82	4.85 (9.5)	
Keyakinin heptaacetate (XXIIIa)	2.05	2.05	2.01	1.80	5.25	*i*
6-*C*-β-D-Glucopyranosyldiosmetin heptaacetate (IIa)	2.07	2.07	2.02	1.81	4.86 (10)	
Miscellaneous C-Glucosyl Compounds (Group C)						
C-β-D-Glucosylbenzene tetraacetate (XXIVa)	2.04	2.03	1.98	1.78	4.36	8
C-β-D-Glucosyldi-*O*-methylphloracetophenone pentaacetate (XXVa)	2.07	2.07	2.04	1.80	*d*	17
Mangiferin octaacetate (XXVIa)	2.07	2.05	2.01	1.79	4.92 (10)	
Aspalathin nonaacetate (XXVIIa)	2.06	2.03	2.00	1.78	4.72 (9–10)	*j*
3,4,2',4',6'-Penta-*O*-methylaspalathin tetraacetate (XXVIIIa)	2.09	2.06	2.03	1.78	5.34 (9–10)	*j*
Isohemiphloin heptaacetate (XXIXa)	2.03	2.03	2.00	1.80	~5.4	8
Hemiphloin heptaacetate (XXXa)	2.05	2.05	2.03	1.83	*d*	8
Combined ranges for groups B and C	(2.03–2.08)	(2.03–2.07)	(1.98–2.04)	(1.77–1.83)		
Other Compounds						
D-Glucose 2,3,4,6-tetraacetate	2.10	2.10	2.03	2.02	...	
Puerarin hexaacetate (XXXIa)	2.07	2.07	2.05	1.72	*d*	8

[a] Spectra from this laboratory were determined at 30–35°; spectra quoted from the literature are assumed to be at about the same temperature. Tetramethylsilane was used as internal standard. [b] Numbers are text references. [c] This band is split, the other branch occurring at δ 2.03. [d] Not reported. [e] This band is split, but the other branch was not clearly discernible at this temperature. [f] Insufficient sample was available to discern this proton clearly. [g] See ref 12. [h] A detailed temperature study of the splitting of this and other bands in the spectrum is given in ref 9. [i] W. E. Hillis, and D. H. S. Horn, *Aust. J. Chem.*, 19, 705 (1966). [j] B. H. Koeppen and D. G. Roux, *Tetrahedron, Lett.*, 3497 (1965); *Biochem. J.*, 99, 604 (1966).

TABLE IV
CHEMICAL SHIFT OF AROMATIC AND METHOXYL PROTONS OF ACETYLATED FLAVONES IN DEUTERIOCHLOROFORM[a]

Compd	Chemical shift and coupling [δ, ppm (J, Hz)] H-3	H-6	H-8	H-2'	H-6	H-3'	H-5'	CH_3O
Apigenin triacetate (VIa)	6.61	6.86 (2.5)	7.35 (2.5)	7.87 (8.5)	7.87 (8.5)	7.26 (8.5)	7.26 (8.5)	...
Acacetin diacetate (XXXIIa)	6.55	6.84 (2.5)	7.31 (2.5)	7.80 (9)	7.80 (9)	7.00 (9)	7.00 (9)	3.88
Luteolin tetraacetate (VIIa)	6.60	6.86 (2.5)	7.36 (2.5)	7.73 (~2.5)	~7.78 (~2.5, 9)	...	7.36 (9)	...
Chrysoeriol triacetate (VIIIa)	6.58	6.83 (2.5)	7.33 (2.5)	~7.38 (~2.5)	~7.45 (~2.5, 9)	...	7.13 (9)	3.90
Diosmetin triacetate (IXa)	6.55	6.83 (2.5)	7.33 (2.5)	7.56 (2.5)	7.71 (~2.5, 8)	...	7.05 (8)	3.90
6-*C*-β-D-Glucosyldiosmetin heptaacetate (IIa)	6.54	...	7.33	7.53 (~2)	7.71 (~2, 8.5)	...	7.06 (8.5)	3.90
Vitexin heptaacetate (Xa)	6.70[b]	6.84[b]	...	8.11; 7.95 (~9)[c]	8.11; 7.95 (~9)[c]	7.40 (9)	7.40 (9)	...
Isovitexin heptaacetate (XIa)	6.65	...	7.38	7.90 (9)	7.90 (9)	7.30 (9)	7.30 (9)	...

[a] Tetramethylsilane used as internal standard, temperature 30–35°. [b] Broad, poorly defined band. [c] H-2' and H-6' are nonequivalent at this temperature.

apigenin nucleus. We tentatively conclude that IV is 6,8-di-*C*-glycosylapigenin.

A number of flavones that are considered to be 6,8-di-*C*-glycosyl derivatives are known.[18,19] One of these, vicenin-2,[20] obtained from *Vitex lucens*, is thought to be a 6,8-di-*C*-glycosylapigenin in which the glycosyl residues are identical. A chromatographic comparison of IV with vicenin-2 indicates probable identity.[21] A noncrystalline *C*-glycosylapigenin from

(18) M. K. Seikel and T. J. Mabry, *Tetrahedron Lett.*, 1105 (1965).
(19) L. Horhammer, H. Wagner, L. Rosprim, T. Mabry, and H. Rösler, *ibid.*, 1707 (1965).
(20) M. K. Seikel, J. H. S. Chow, and L. Feldman, *Phytochemistry*, 5, 439 (1966).
(21) Vicenin-2 was isolated from an extract of *Vitex lucens* wood by elution from a thin layer plate. It was not obtained crystalline but its properties correspond with those reported by Seikel and coworkers[20] for vicenin-2.

lemon peel, isolated recently by Chopin,[6] is also considered[1] to be identical with vicenin-2.

Compound V was obtained from lemon peel as an amorphous solid. Ultraviolet spectral data suggest that it is derived from diosmetin, whereas chromatographic and electrophoretic data indicate that it has two glycosyl residues. We regard 6,8-di-*C*-glycosyldiosmetin as a tentative structure for V. It is probably identical with the *C*-glycosyldiosmetin reported by Chopin.[6]

The results described here illustrate again the wide distribution of *C*-glycosylflavones. The presence in the lemon of apigenin *O*-glycoside[22] and 6,8-di-*C*-glycosylapigenin, as well as diosmin,[23] 6-*C*-glucosyldiosmetin, 8-*C*-glucosyldiosmetin, and 6,8-di-*C*-glycosyldiosmetin are interesting examples of the co-occurrence of *O*- and *C*-glycosyl derivatives of the same flavone. As a result of this and earlier isolation studies[22-26] it is known that lemons contain at least twenty different flavonoids or related compounds. It is not clear whether this demonstrates an unusually versatile synthetic capacity of the lemon or merely reflects the fact that this plant has been scrutinized more closely than most.

Experimental Section

Isolation of 8-C-Glucosyldiosmetin (I), 6-C-Glucosyldiosmetin (II), and 6,8-Gi-C-glycosylapigenin (IV) from Lemons.—The isolation procedure has been described in detail in an earlier publication.[24] "Calcium Flavonate Glycoside, Lemon" (a mixture of the calcium salts of crude lemon flavonoids)[27] in aqueous solution at pH 3 was extracted with 1-butanol. Evaporation of the 1-butanol extract gave a mixture of glycosides. The mixture (6 g) was separated into its constituents by chromatographing it on a column of 100 mesh silicic acid (1090 g) developed with methanol–chloroform in a stepwise gradient elution. The progress of the elution was monitored by paper chromatography (10% acetic acid) and uv spectra.

Compound I was eluted at a concentration of 10–11% methanol in chloroform. It followed limocitrin 3-β-D-glucoside.[25] Compound II followed I at a concentration of 11% methanol. Compound IV was eluted at 23–26% methanol, following eriocitrin. All three compounds appeared as dark spots on paper chromatograms under uv light. After assembling fractions and taking them to dryness the products were crystallized (see Table V).

TABLE V

Compd	Solvent	Mp, °C	Yield, mg
I	Methanol	267–268	7
II	Methanol	243–245	15
IV	Water	233–236	2

Acetyl derivatives Ia, IIa, and IVa were prepared by allowing the compounds to stand in acetic acid–pyridine at room temperature, followed by evaporation of the reagents under vacuum. None of the acetyl derivatives could be obtained in crystalline form.

Acid Treatment of Compounds I, II, and IV.—The samples were dissolved in ethanol made 3 *N* in hydrochloric acid by adding the concentrated reagent. The solutions were heated on the steam bath and cooled, the precipitates were filtered, and the filtrate was extracted with ethyl acetate. The ethyl acetate extract and the precipitate were combined and used for paper chromatography in these solvents: 10 and 30% acetic acid, butanol–acetic acid–water, and ethyl acetate–formic acid–water (see Table II). The chromatograms showed that compound I was partially converted into II after 5 hr of heating; compound II was partially converted into I after 1 hr; and compound IV remained essentially unchanged after 1 hr.

Alkaline Hydrolysis of Compounds I and II.—The acetyl derivatives Ia and IIa (about 5 mg each) were boiled in 40% aqueous potassium hydroxide (1 ml) for 45 min. The products were worked up in the usual way and chromatographed on paper with benzene–acetic acid–water (2:2:1 upper phase). Isovanillic acid was identified in both runs by its R_f value (0.54).

Isolation of 6,8-Di-C-glycosyldiosmetin (V) from Lemons.—"Lemon Bioflavonoid Complex"[27] (100 g) was extracted with boiling methanol. Evaporation of the methanol gave 63 g of crude glycosides. This was dissolved in water (500 ml) and the solution adjusted to pH 4.65. Crude fungal hemicellulase[28] (15 g) was added and the mixture kept at room temperature for 3 days. It was then extracted with four 50-ml portions of ether and ten 50-ml portions of ethyl acetate to remove flavonoid aglycones formed by hydrolysis of *O*-glycosides.

The remaining aqueous layer was concentrated under vacuum to a volume of 100 ml and this was diluted with 500 ml of methanol. The voluminous precipitate was centrifuged down and discarded. The supernatant was taken to dryness and the residue (47 g) was dissolved in water (120 ml) and extracted for 2 days with ethyl acetate in a liquid–liquid extractor. The aqueous layer was extracted with fifteen 30-ml portions of 1-butanol, the combined butanol extract was taken to dryness, and the residue was redissolved in water (40 ml) and reextracted with ten 25-ml portions of 1-butanol. This yielded a residue of 7 g, which was dissolved in 50% methanol (50 ml) and treated with 30% aqueous basic lead acetate (20 ml). The filtered precipitate was treated with hydrogen sulfide in the usual way to give 2.2 g of partially purified flavonoids. This material was further purified on a polyamide column (3.7 × 27 cm) eluted with 10–15% aqueous methanol. Evaporation of the eluate gave a residue of 0.7 g which was adsorbed in the usual way (see experiment below on isolation of I and II from oranges) onto 4 g of 100 mesh silicic acid. The dry powder containing the adsorbed flavonoids was slurried with ethyl acetate (25 ml) and this was added to the top of a 3.7 × 30 cm column of silicic acid prepared in ethyl acetate. The compounds were eluted with methanol–ethyl acetate using a stepwise gradient elution. 6,8-Di-*C*-glycosylapigenin (IV) was eluted when the concentration of methanol reached 12%; it crystallized from water (5 mg, mp 236°). 6,8-Di-*C*-glycosyldiosmetin (V) was eluted at a concentration of 13% methanol. The assembled fractions containing V were taken to dryness and the residue was dissolved in ethanol from which it precipitated as a gel (7 mg). Attempts to crystallize V and its acetyl derivative Va (prepared in hot acetic anhydride–pyridine) were unsuccessful.

Isolation of 8-C-Glucosyldiosmetin (I) and 2″-*O*-β-D-Xylosylvitexin (III) from Oranges.—"Orange Bioflavonoid Complex, Navel"[27] (25 g) was extracted with two 250-ml portions of chloroform under reflux and then with hot ethanol (100 ml). Evaporation of the ethanol afforded 16 g of crude glycosides. The glycosides (10 g) in methanol (100 ml) were adsorbed onto 100 mesh silicic acid (55 g) by adding the silicic acid in portions with shaking and finally evaporating under vacuum at room temperature to a dry powder. The dry powder was shaken with 100-ml portions of chloroform until the extracts were colorless. It was then slurried in chloroform and introduced to the top of an 8 × 71 cm column of silicic acid (1750 g) which had been prepared as a slurry in chloroform (7000 ml). The compounds were separated by methanol–chloroform in a stepwise gradient elution.

Compound I was eluted together with a blue fluorescing impurity at 18–20% methanol. It crystallized in very low yield from methanol and was identical in every respect (melting point, R_f, and ir and uv spectrum) with compound I obtained from lemons.

Compound III, accompanied by a moderate amount of naringenin 7-β-rutinoside,[29] was eluted with 24–25% methanol. It appeared as a dark spot on paper chromatograms under uv light. Assembled fractions containing III were extracted with several portions of ethyl acetate which removed most of the

(22) R. M. Horowitz and B. Gentili, *J. Org. Chem.*, **26**, 2183 (1960).
(23) R. M. Horowitz, *ibid.*, **21**, 1184 (1956).
(24) R. M. Horowitz and B. Gentili, *J. Amer. Chem. Soc.*, **82**, 2803 (1960).
(25) R. M. Horowitz and B. Gentili, *J. Org. Chem.*, **26**, 2899 (1961).
(26) B. Gentili and R. M. Horowitz, *Tetrahedron*, **20**, 2313 (1964).
(27) Manufactured by Sunkist Growers, Ontario, Calif. References to specific products or brands does not constitute endorsement by the U. S. Department of Agriculture.
(28) Crude preparations of the enzyme give better results in the hydrolysis than purified preparations.
(29) E. Gentili and R. M. Horowitz, *Bull. Nat. Inst. Sci. India*, No. 31, 78 (1965).

accompanying naringenin rutinoside. Compound III failed to crystallize, even when seeded with crystalline 2''-*O*-β-D-xylosylvitexin obtained from *Vitex lucens*. It was freely soluble in water. Compound III was indistinguishable from 2''-*O*-β-D-xylosylvitexin on paper chromatography in a variety of solvents or on paper electrophoresis (Table II). The two compounds were also indistinguishable (R_f = 0.18) on polyamide tlc using nitromethane–methanol (2:1).

Hydrolysis of 2''-*O*-β-D-Xylosylvitexin (III).—A sample of compound III in aqueous 2 *N* hydrochloric acid was heated on the steam bath for 30 min. The solution was extracted with ethyl acetate. Evaporation of the extract afforded a mixture of vitexin and isovitexin, as shown by paper chromatography and electrophoresis. When the hydrolysis was carried out enzymatically at pH 4.6 using crude hemicellulase,[28] the ethyl acetate extract contained mainly vitexin together with a very small proportion of isovitexin. The presence of xylose in the aqueous layers remaining from these hydrolyses was demonstrated by paper chromatography.

Registry No.—I, 15822-81-8; Ia, 15895-78-0; II, 15822-82-9; IIa, 15895-77-9; III, 11044-10-3; VI, 520-36-5; VIa, 3316-46-9; VII, 491-70-3; VIIa, 1061-93-4; VIII, 491-71-4; VIIIa, 3162-04-7; IX, 520-34-3; IXa, 3162-05-8; X, 1397-60-0; Xa, 11040-83-8; XI, 11044-04-5; XIa, 11044-05-6; XIVa, 11044-08-9; XVa, 11044-03-4; XVIIa, 11044-09-0; XXIIa, 11044-06-7; XXVa, 6980-38-7; XXVIa, 11044-07-8; XXXIIa, 5892-39-7; D-glucose 2,3,4,6-tetraacetate, 10343-06-3.

Dihydroisocoumarins from a *Sporormia* Fungus

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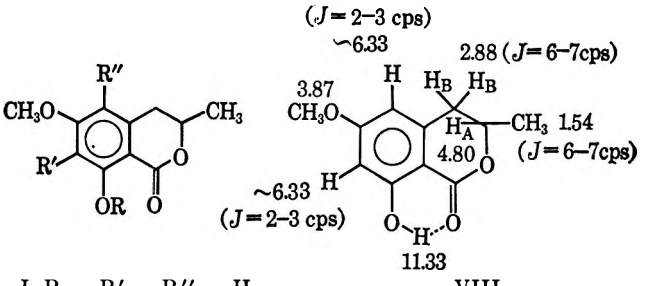
Three dihydroisocoumarins, 3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin, 5,7-dichloro-3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin, and 7-chloro-3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin, have been isolated from a *Sporormia* fungus. The structures of the two new chlorinated dihydroisocoumarins have been established by spectral studies and by chemical conversion.

Sondheimer[1] isolated 3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin (I) from carrots which had developed a bitter taste during storage. Condon, *et al.*,[2-4] later associated the production of this fungitoxic substance in carrots with alterations in the normal metabolism of the carrot root tissue which they felt were possibly induced by the presence of fungi. Recently, Aue, *et al.*,[5] have reported the isolation of this same compound, which is sometimes referred to as 6-methoxymellein, from a submerged culture of the fungus *Sporormia bipartis* Cain. In our work on the metabolic products of *Sporormia affinis* Sacc., Bomm and Rouss, we have isolated not only 6-methoxymellein (I) but also the closely related halogenated compounds 5,7-dichloro-3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin (IV) and 7-chloro-3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin (V).

These findings and those of Aue, *et al.*,[5] suggest to us that the occurrence of I in fungal infected carrots might be due to the fungus itself. The presence of I in two *Sporormia* species may also be noteworthy in a chemotaxonomic sense.

For our purposes, the fungus *Sporormia affinis* was grown in submerged culture under standard conditions and the metabolic products were isolated after 120 hr by carbon adsorption followed by chromatography. A major product was identical in its physical and chemical properties with 6-methoxymellein; its identity was confirmed by comparison with an authentic specimen.[1]

In determining the structure of the two minor chlorinated metabolites, the nmr and mass spectra of I were quite revealing and it is appropriate to discuss them at this stage. The various peaks in the nmr spectrum are assigned pictorially in formula VIII.



VIII

I, R = R′ = R″ = H
II, R = CH_3; R′ = R″ = H
III, R = CH_3; R′ = R″ = Cl
IV, R = H; R′ = R″ = Cl
V, R = R″ = H; R′ = Cl
VI, R = CH_3; R′ = Cl; R″ = H
VII, R = CH_3; R′ = H; R″ = Cl

The three-proton doublet at 1.54 ppm (J = 6–7 cps) is attributed to the methyl group on the carbon bearing a single proton and attached to the electronegative oxygen. A doublet at 2.88 ppm is assigned to the virtually equivalent methylene protons H_B split by the single proton H_A of the asymmetric center. A sharp three-proton singlet at 3.87 ppm is due to the methoxy group and the one-proton multiplet at 4.80 ppm arises from the coupling of the methyl and methylene group with the single proton H_A. The aromatic region contains split signals (J = 2–3 cps typical for *meta*-coupled protons) for two barely separated protons at about 6.33 ppm and the exchangeable proton of the intramolecularly bonded hydroxyl group is observed at 11.33 ppm. The mass spectrum confirms the molecular weight by a peak at m/e 208 and contains a number of other significant peaks. The most abundant peak at m/e 164 (400%) arises because of loss of acetaldehyde. A metastable peak at 129.3 mass units confirms this loss from the molecular ion. The loss of $CH_3CO\cdot$ accounts for the peak at m/e 165 (100%). Elimination of CO from the molecular ion of I occurs as is evidenced by m/e 180 (9%) but is clearly not a

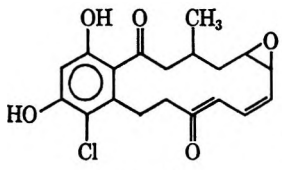
(1) E. Sondheimer, *J. Amer. Chem. Soc.*, **79**, 5036 (1957).
(2) P. Condon and J. Kuc, *Phytopathology*, **50**, 267 (1960).
(3) P. Condon and J. Kuc, *ibid.*, **52**, 182 (1962).
(4) P. Condon, J. Kuc, and M. H. Draudt, *ibid.*, **53**, 1244 (1963).
(5) R. Aue, R. Mauli, and R. P. Sigg, *Experientia*, **22**, 575 (1966).

significant feature.[6] Expulsion of CO from this system seems to be largely replaced by a fragmentation where 29 mass units (CHO) are removed to give the peak *m/e* 179 (49%). Our data are suggestive that the hydrogen of this fragment does not seem to come, as might be expected, entirely from the phenolic group, but may in part also come from the adjacent aromatic position. When the adjacent proton is replaced by chlorine, as in the case of the other metabolites, the loss of CHO is roughly halved while loss of elements COCl is then observed in about the same abundance. On the other hand, the data so far available does not rule out the sequential loss of CO and Cl.

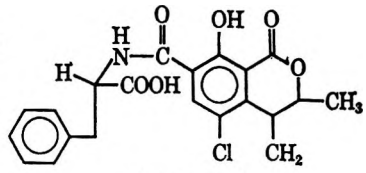
The second compound isolated from the *Sporormia* fermentation melts at 225–226° and has a molecular formula of $C_{11}H_{10}O_4Cl_2$ (compound IV). The material is optically active and has low solubility in ether but is readily soluble in ethyl acetate, chloroform, acetone, and the lower alcohols. It can be extracted from its chloroform solution by 5% aqueous bicarbonate solution and gives a positive ferric chloride test. It does not form a methyl ether with diazomethane but it is converted into this derivative by using a mixture of sodium hydroxide and dimethyl sulfate. In the infrared spectrum of the dichloro compound a carbonyl peak is observed at 1695 cm^{-1}, whereas in the methyl ether of the material, this carbonyl peak is shifted to 1737 cm^{-1}. These features are consistent with the behavior of a substance containing a chelated phenolic group.[7] The ultraviolet spectrum of compound IV shows peaks at 224, 260, and 310 mμ. In alkaline solution the low wavelength absorption undergoes a bathochromic shift to 244; the peak at 260 is obliterated while a large hyperchromic effect is observed at 310 mμ. These changes are reversed upon neutralization of the alkaline solutions. The ultraviolet absorption characteristics of the compound were strongly reminiscent of those of I and the close relationship between the two compounds was further confirmed by nmr spectral data.

The nmr spectrum of the dichloro metabolite contains a doublet at 1.55 ppm (J = 6–7 cps) assignable to a methyl group split by a single proton. Instead of a doublet at 2.88 as is observed in the spectrum of I there is a multiplet centered at 2.95 ppm. In the chloro compound the nonequivalence of the methylene protons is enhanced because of the *peri* effect of the chlorine atom at the 5 position in the aromatic ring. The three-proton signal due to the methoxy group appears at 3.92 ppm exactly as with 6-methoxymellein. The single proton of the asymmetric center now gives rise to a complex multiplet at 4.58 ppm. The extra splitting in this case, as opposed to the much less complicated multiplet at 4.80 ppm in the spectrum of I, again arises because of the enhanced nonequivalence of the methylene protons in the dichloro metabolite.

A similar nonequivalent benzylic methylene group was observed by McCapra, *et al.*,[8] and Mirrington and others[9] in their work on monorden and by Van den Merwe and his group in their identification of the



monorden



ochratoxin A

ochratoxins.[10] The mass spectrum of IV, while not as definitive as that of I, nevertheless substantiates the chlorinated dihydroisocoumarin structure. The molecular ion peak at 276, 83% (*m/e* 215 taken as 100%) together with peaks at 278 (56%) and 280 (10%) are in good agreement with Beynon's postulates for doubly chlorinated compounds.[11] Large significant peaks at 233 (38%) and 232 (82%) are attributable to the loss of $CH_3CO\cdot$ and acetaldehyde which are characteristic fragments of the 3-methyldihydroisocoumarin structure. No peak is observed for the loss of CO but there are fragments representing the loss of CHO *m/e* 247 (16%) and COCl *m/e* 213 (14%).

The dechlorination of the aromatic ring of tetracycline compounds by catalytic hydrogenation is well known.[12] It was felt that this technique might be used to convert the chlorinated metabolite into 6-methoxymellein after first protecting the phenolic group as the methyl ether. However, in our hands, this approach did not prove fruitful. Another procedure, that of converting the methyl ether of 6-methoxy mellein (II) into the corresponding dichloro derivative III by direct chlorination was successful. Whalley's method,[13] using a mixture of sulfuryl chloride and aluminum chloride, converted II into a monochlorinated derivative which we obtained in small quantity and believe is the 5-chloro compound VII. An older procedure, using sulfuryl chloride together with a solution of aluminum chloride in sulfur monochloride[14] resulted in the chlorination of the two open positions of the aromatic ring. The product has an identical melting point and infrared spectrum with those of the methyl ether III of the natural product.

The monochlorinated metabolite isolated from *S. affinis* fungus is a white, optically active, crystalline material which melts at 169–170° and has the empirical formula $C_{11}H_{11}O_4Cl$. The material is sparingly soluble in ether and in 5% bicarbonate solution but readily soluble in ethyl acetate, chloroform, and the lower alcohols and gives a positive ferric chloride test. The ultraviolet spectrum in methanol has peaks at 224, 272, and 305 mμ. In alkaline solution the lower absorbance peak undergoes a red shift to 230 mμ; the peak at 272 mμ exhibits a hypsochromic effect while the third absorbance maximum is shifted to 340 mμ and in addition displays a hyperchromic effect. As in the case of the other two metabolites, all of these changes are reversed upon acidification.

The infrared spectrum shows a strong carbonyl absorption at 1645 which is shifted to 1720 cm^{-1} upon

(6) J. P. Kutney, G. Eigendorf, D. L. Dreyer, and L. A. Mitscher, *Can. J. Chem.*, in press.

(7) T. M. Meijer and H. Schmid, *Helv. Chim. Acta*, **31**, 1603 (1948).

(8) F. McCapra, A. I. Scott, P. Delmotte-Plaquee, and N. S. Bhacca, *Tetrahedron Lett.*, 869 (1964).

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(10) K. J. Van den Merwe, P. S. Steyn, and L. Tourie, *J. Chem. Soc.*, 7083 (1965).

(11) J. H. Beynon, "Mass Spectrometry and Its Application to Organic Chemistry," Elsevier Publishing Co., Amsterdam, 1960, p 298.

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(13) J. S. E. Holker, W. J. Ross, J. Staunton, and W. B. Whalley, *J. Chem. Soc.*, 4150 (1962).

(14) O. Silberrad, *ibid.*, 1015 (1922).

formation of the methyl ether. The similarities in the ultraviolet and infrared spectra of the three metabolites indicated that all three are closely related structurally. It was felt that the third product had the 3-methyldihydroisocoumarin structure with a chlorine atom in either the 5 or the 7 position. The nmr spectral data clearly indicated that the chlorine is in the 7 position and, hence, the structure of the product is 7-chloro-3-methyl-6-methoxy-8-hydroxy-3,-4-dihydroisocoumarin (V). The nmr spectrum of V is identical with that of 6-methoxymellein (I) except in the aromatic region where V exhibits a one-proton singlet at 6.33 ppm. The methylene protons of V are virtually equivalent as in I demonstrating the lack of a *peri* effect and, hence, the chlorine atom cannot occupy the 5 position.

The mass spectrum of V has large peaks at *m/e* 199 (72%) and 198 (108%) (*m/e* 242 taken as 100%) accounted for by loss of $CH_3CO\cdot$ and CH_3CHO, respectively. Presence of metastable peaks at approximately 162 and 146 mass units confirm the acetaldehyde fragmentation. The former accounts for the loss of CH_3CHO from the molecular ion and the latter arises because of the loss of water from the resultant fragment (198 − 18) → 180 = 146. The excision of CHO *m/e* 213 (16%) and COCl *m/e* 179 (16%) is also noted as in the case of the dihalo compound.

Some difficulty was encountered in forming the methyl ether of V. Use of dimethyl sulfate and sodium hydroxide failed to methylate this material although these reagents worked satisfactorily with compounds I and IV. Refluxing of the material in acetone with iodomethane and sodium carbonate[15] also failed to effect the desired reaction. The methyl ether was prepared by the method of Garden and Thomson[16] using silver oxide and methyl iodide in chloroform. All three metabolites exhibited low potency antifungal activity.

Experimental Section

Nmr spectra were run on a Varian A60 instrument under normal conditions. Mass spectra were run on an AE I MS9 high-resolution, direct-inlet mass spectrometer.

3-Methyl-6-methoxy-8-hydroxy-3,4-dihydroisocourmarin (I).—*Sporomia affinis* Sacc., Bomm and Rouss (Lederle culture N313), was deep-fermented using standard conditions of agitation and aeration for 120 hr at 28° on a medium consisting of 2.0 g of molasses, 1.5 g of corn starch, 1.0 g of cerelose, 0.75 g of soya peptone, 0.5 g of calcium carbonate, and 0.25 g of prograsol[17] per liter of water. The whole mash was filtered and filtrate was treated with 10% w/v of charcoal. The charcoal pad was eluted with acetone–water (90:10) at pH 2.0 and the eluate concentrated to the aqueous phase which was extracted with chloroform. The chloroform extracts were concentrated to a gum which was chromatographed over silica gel (Davidson Grade 923) using chloroform–hexane (1:1) as developing solvent. The less polar fraction from the adsorption column was partitioned over diatomaceous earth using the partitioning system hexane–ethyl acetate–methanol–water (85:15:15:6). The material eluting in the second holdback volume was recrystallized from ether–hexane to obtain I in yields of up to 22 mg per liter of mash: mp 75.5–76°; $[\alpha]^{25}D$ −51.0 ± 3.0 (*c* 1.50 MeOH) (lit.[1] mp 75–76°; $[\alpha]^{24}D$ −56.0 [*c* 1.0, MeOH]); λ_{max} (MeOH) 302 mμ (ε 4890), 267 (12,580), and 216 (19,860); ν_{max} (KBR) 1665, 1630, 1580, 1375, 1245, 1205, 1160, 1115, 1090, 1070, 1038, 965, 850, 828, 800, and 707 cm^{-1}; nmr ($CDCl_3$) at δ 1.54 ($-CH_3$, doublet, *J* = 6–7 cps), 2.88 ($-CH_2-$, doublet, *J* = 6–7 cps), 3.87 ($-OCH_3$, singlet), 4.80 (>CH–, multiplet), 6.33 (aromatic 2 H, split singlets, *J* = 2–3 cps), and 11.33 (–OH, exchangeable singlet).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; mol wt, 208. Found: C, 63.30; H, 5.69; mol wt, 208 ± 0 (mass spectroscopy).

3-Methyl-6,8-dimethoxy-3,4-dihydroisocoumarin (II).—The methyl ether of I was prepared as described by Sondheimer[1] in 50% yield following recrystallization from ethyl acetate–hexane: mp 125–126°; $[\alpha]^{25}D$ −152 ± 2.8° (*c* 1.05); λ_{max} (MeOH) 297 mμ (ε 6210), 263 (13,540), and 214 (23,530); ν_{max} (KBR) 1710, 1600, 1463, 1343, 1250, 1198, 1163, 1115, 1084, 1043, 855, and 790 cm^{-1}; nmr ($CDCl_3$) at δ 1.42 ($-CH_3$, doublet, *J* = 6–7 cps), 2.80 ($-CH_2-$, doublet, *J* = 6–7 cps), 3.83 ($-OCH_3$, singlet), 3.90 ($-OCH_3$, singlet), 4.45 (>CH–, multiplet), 6.33 (aromatic 2 H, split singlets, *J* = 2–3 cps).

Professor Sondheimer was kind enough to forward us a sample of the methyl ether of 6-methoxymellein. The melting point and infrared curve of this material were identical with those of II.

5,7-Dichloro-3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin (IV).—This metabolite was obtained by following the isolation procedure described for I up to the point of extraction of the concentrated charcoal eluate with chloroform. The chloroform extract was back extracted with 10% sodium bicarbonate solution. The bicarbonate extract was acidified and extracted three times with chloroform. The chloroform extracts were dried over anhydrous magnesium sulfate and concentrated to an oil which was allowed to stand at room temperature for 3–4 days, during which time a solid formed. Trituration of the oil–solid mixture with a little ether gave a suspension which could be filtered to get the solid residue. Recrystallization from ethyl acetate–hexane yielded IV: mp 225–226°; $[\alpha]^{25}D$ −142.0 ± 2.8 (*c* 1.067, MeOH); λ_{max} (MeOH) 310 mμ (ε 5540), 260 (7890), and 224 (24,830); λ_{max} (methanolic 0.1 *N* NaOH) 310 mμ (ε 28,060) and 244 mμ (ε 17,300); ν_{max} (KBR) 1695, 1575, 1425, 1410, 1355, 1260, 1115, 1095, 960, 798, 790, 775, and 738 cm^{-1}; nmr ($CDCl_3$) at δ 1.55 ($-CH_3-$ doublet, *J* = 6–7 cps), 2.88 ($-CH_2-$, multiplet), 3.92 ($-OCH_3$, singlet), 4.58 (>CH–, multiplet).

Anal. Calcd for $C_{11}H_{10}O_4Cl_2$: C, 47.65; H, 3.63; O, 23.10; Cl, 25.63; mol wt, 277. Found: C, 48.05; H, 3.44; O, 24.15; Cl, 24.95; mol wt, 276 ± 0 (mass spectroscopy).

Yields of the crystalline product were of the order 0.5–1.0 mg per liter of mash. In cases where the amount of IV present was small and hence it failed to crystallize after 3–4 days as described, it was necessary to pass the oil over silica gel. Elution was carried out using chloroform–hexane (50:50) and the material which was recovered from the fifth through seventh holdback volumes was partitioned over diatomaceous earth using hexane–ethyl acetate–methanol–water (85:15:15:6). Compound IV was eluted in the first three to four holdback volumes, whereas V came off in the eighth through eleventh volumes. This was a little unexpected since IV is a stronger acid than V and hence should be a more polar material.

5,7-Dichloro-3-methyl-6,8-dimethoxy-3,4-dihydroisocoumarin (III). A. Chlorination of 3-Methyl-6,8-dimethoxy-3,4-dihydroisocoumarin.—In our first attempt to chlorinate II we followed Whalley's procedure.[9] To a solution of 150 mg (0.67 mmol) of 3-methyl-6,8-dimethoxy-3,4-dihydroisocoumarin (II) in 20 ml of carbon tetrachloride 0.1 ml of sulfuryl chloride was added followed by 100 mg of aluminum trichloride. The mixture was allowed to stand at room temperature overnight. Work-up yielded a yellowish oil which was passed over 10 g of acid-washed silica gel by elution with ethyl acetate–hexane (20:80). The material which came off in first and second holdback volumes was recrystallized from ethyl acetate–hexane to get 25 mg of product, mp 119–120°, which gave the elemental analysis of a monochlorinated compound: ν_{max} (KBR) 1725, 1598, 1460, 1425, 1375, 1230, 1205, 1107, 1050, 925, 802, 772, and 750 cm^{-1}.

Anal. Calcd for $C_{12}H_{13}O_4Cl$: C, 56.14; H, 5.07; Cl, 13.83. Found: C, 56.70; H, 5.11; Cl, 13.74.

It is likely that this material is the compound 5-chloro-3-methyl-6,8-dimethoxy-3,4-dihydroisocoumarin as it is isomeric with product VI, although this conclusion has not been verified.

Using the method of Silberrad[10] it was possible to obtain the desired product in good yield. The chlorinating agent, consisting of 1 ml of sulfuryl chloride together with 0.1 ml of sulfur monochloride and 10 mg of aluminum trichloride, was first prepared to give a reddish mixture. To this, 100 mg (0.45 mmol) of the

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(16) J. F. Garden and R. H. Thomson, *J. Chem. Soc.*, 2483 (1957).

(17) Distillers grain solubles from corn; Publicker Industries, Inc., Philadelphia, Pa.

methyl ether of 6-methoxymellein (II) were added directly. The crystals dissolved instantly with the evolution of gas bubbles. The resulting red solution was evaporated under reduced pressure to an oil–solid mixture which was triturated with ether and about 40 mg of a water-soluble solid were filtered off. The ether solution was concentrated to an oil and chromatographed over 10 g of acid grade Woelm alumina and eluted with ethyl acetate–hexane (1:10). The material obtained from the first holdback volume weighed 95 mg. After several recrystallizations from ether–hexane and ethyl acetate–hexane, 50 mg of white product was obtained: mp 81.5–82°; $[\alpha]^{25}D$ −160 ± 2.9 (*c* 1.037, MeOH); λ_{max} (MeOH) 305 mμ (ε 1740), 252 (6530), and 220 (33,350); ν_{max} (KBR) 1735, 1565, 1455, 1405, 1377, 1337, 1250, 1125, 1096, 1050, 980, 955, 930, 793, 765, and 747 cm^{-1}; nmr ($CDCl_3$) at δ 1.55 ($-CH_3$, doublet, J = 6–7 cps), 2.92 ($-CH_2-$, multiplet), 3.97 ($-OCH_3$, singlet), 4.00 ($-OCH_3$, singlet), 4.50 (>CH–, multiplet).

Anal. Calcd for $C_{12}H_{12}O_4Cl_2$: C, 49.48; H, 3.78; Cl, 24.39. Found: C, 50.10; H, 3.96; Cl, 24.44.

B. Methylation of 5,7-Dichloro-3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin.—Approximately 40 mg (0.15 mmol) of IV were added to 0.3 ml of dimethyl sulfate, and 4 *N* sodium hydroxide was added dropwise until the mixture gave an alkaline reaction. The suspension was heated on a steam bath for 15 min. Tlc on Eastman sheets (type K301R) using hexane–ethyl acetate (60:40) indicated that the methyl ether had formed. The solution was acidified with dilute HCl and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate and concentrated to an oil which was chromatographed over 7.5 g of silica gel to give a nonpolar fraction which, on recrystallization from ethyl acetate–hexane, yielded 20 mg of product, mp 81.5–82°. The infrared spectrum of this material was identical with that of the product obtained by method of Silberrad. The congruency of these materials is conclusive proof of the identity of this metabolite since 6,8-dimethoxymellein is known.

7-Chloro-3-methyl-6-methoxy-8-hydroxy-3,4-dihydroisocoumarin (V).—Submerged fermentation of the *S. affinis* as described under the isolation of I was handled in the manner described up to the point of extraction of the concentrated charcoal eluate. The eluate was extracted with ether and the combined extracts were concentrated to an oil which was chromatographed over acid-washed silica gel and eluted with chloroform–hexane (75:25). The material eluting in the seventh through twelfth holdback volumes was partitioned over diatomaceous earth using the system hexane–ethyl acetate–methanol–water (85:15:15:6). The material which came off in the first and second holdback volumes consisted of a mixture of I and V. The two materials were then separated cleanly by chromatography over silica gel using hexane–ethyl acetate (95:5) as eluting solvent. Compound I was obtained from the fifth through seventh holdback volumes; V was recovered from the eleventh through thirteenth holdback volumes. Following recrystallization from ethyl acetate–hexane the yields of crystalline product V were in the range 0.0–0.5 mg per liter of mash: mp 170–171°; $[\alpha]^{25}D$ −71.3 ± 5.9 [c 0.505, MeOH]; λ_{max} (MeOH) 305 mμ (ε 680), 272 (12,600), and 224 (25,400); λ_{max} (methanolic 0.1 *N* NaOH) 340 mμ (ε 6420), 272 (25,000), and 224 (29,700); ν_{max} (KBR) 1645, 1565, 1512, 1423, 1380, 1325, 1285, 1265, 1210, 1205, 1150, 1120, 1093, 1030, 935, 908, 833, 803, 784, 760, and 700 cm^{-1}; nmr ($CDCl_3$) at δ 1.50 ($-CH_3$, doublet, J = 6–7 cps), 2.88 ($-CH_2-$, doublet, J = 6–7 cps), 3.97 ($-OCH_3$, singlet), 4.70 (>CH–, multiplet), 6.33 (aromatic 1 H, singlet), and 11.17 (–OH, exchangeable singlet).

Anal. Calcd for $C_{11}H_{11}O_4Cl$: C, 54.43; H, 4.53; Cl, 14.64; mol wt, 242.5. Found: C, 54.48; H, 4.95; Cl, 14.68; mol wt, 242 ± 0 (mass spectroscopy).

7-Chloro-3-methyl-6,8-dimethoxy-3,4-dihydroisocoumarin (VI).—Attempts to methylate V using dimethyl sulfate and sodium hydroxide solution failed. Since IV was methylated by this procedure no trouble had been anticipated. Approximately 70 mg (0.29 mmol) of V were dissolved in 0.5 ml of dimethyl sulfate and 4 N sodium hydroxide was added dropwise until the reaction mixture gave an alkaline reaction. The mixture was then heated on the steam bath for 15 min and allowed to sit overnight at room temperature. Work-up of the suspension yielded a solid which was chromatographed over silica gel, and eluted with chloroform to yield 40 mg of material, mp 130–131.5° with a trace persisting to 135°. The infrared curve of this material indicated that the isocoumarin ring had suffered some decomposition. Refluxing of V in acetone with anhydrous sodium carbonate and an excess of iodomethane for several hours[14] resulted, upon work-up, in recovery of starting material. The best method for the methylation of these chelated phenolic compounds appears to be that of Garden and Thomson.[15] To a solution of 40 mg (0.16 mmol) of V in 2 ml of chloroform approximately 100 mg of moist silver oxide were added together with 2 ml of iodomethane and the suspension stirred at room temperature for 1 hr. Tlc and ferric chloride testing at this stage showed the reaction to be incomplete and another 100 mg of silver oxide and 2 ml of iodomethane were added and stirring was continued for another hour by which time reaction was finished. The silver oxide was filtered off to give a colorless solution which on concentration yielded white crystals. Recrystallization from ethyl acetate–hexane gave 35 mg: mp 160.5–161.5°; $[\alpha]^{25}D$ −137 ± 10° (*c* 0.300, MeOH); λ_{max} (MeOH) 265 mμ (ε 12,610) and 220 mμ (ε 24,460); ν_{max} (KBR) 1720, 1595, 1450, 1408, 1370, 1353, 1310, 1262, 1216, 1206, 1185, 1117, 1105, 1064, 990, 933, 912, 858, 798, and 778 cm^{-1}; nmr ($CDCl_3$) at δ 1.45 ($-CH_3$, doublet, J = 6–7 cps), 2.83 ($-CH_2-$, doublet, J = 6–7 cps), 3.95 (2 × $-OCH_3$, singlet), 4.47 (>CH–, multiplet), and 6.63 (aromatic 1 H, singlet).

Anal. Calcd for $C_{12}H_{13}O_4Cl$; C, 56.14; H, 5.07; Cl, 13.83. Found: C, 56.46; H, 5.02; Cl, 13.71.

Registry No.—I, 13410-15-6; II, 15766-71-9; III, 15815-77-7; IV, 15815-78-8; V, 15815-79-9; VI, 15815-80-2; VII, 15815-81-3.

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Synthesis of a Protected C-Terminal δ-Aminovaleric Acid Analog of the Peptide Sequence Occurring at Positions 11–19 in Adrenocorticotropins[1a]

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The protected nonapeptide, N^{α}-carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysylprolylvalylglycyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric acid methyl ester, has been synthesized by a stepwise procedure. The nonapeptide corresponds to the sequence of amino acids occurring at positions 11–19 in the adrenocorticotropic hormone (ACTH) molecule, but possesses the δ-aminovaleric acid as its terminal residue instead of the proline residue occurring at position 19 in the native hormone.

Recent studies carried out in this laboratory[2] revealed that exposure of certain esters of proline, which are commonly used in peptide synthesis, to treatment with sodium in liquid ammonia, can lead to cleavage of the proline ring with the formation of the corresponding δ-aminovaleric acid derivative, provided that the proline imino group is acylated as in the case of peptides containing a proline ester at the C terminus. Insofar as this reaction can provide a novel route for the preparation of peptides containing a C-terminal δ-aminovaleric acid residue from the corresponding proline ester analogs, it was considered of importance to undertake the direct synthesis of such peptides which can serve as reference compounds in planned future studies on this aspect of the sodium–liquid ammonia procedures. Being part of a series of synthetic studies[3–5] on the N-terminal portion of the ACTH molecule, this paper describes the synthesis of the protected nonapeptide N^{α}-carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysylprolylvalylglycyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric acid methyl ester (IX, Figure 1).[6] In this peptide which corresponds to the sequence of amino acid residues occurring at positions 11–19 in ACTH, δ-aminovaleric acid residue is substituted for the proline residue occurring at position 19 in the native hormone.

δ-Aminovaleric acid hydrochloride (I) was readily converted into the corresponding crystalline methyl ester II by means of 2,2-dimethoxypropane in the presence of concentrated hydrochloric acid.[7] Compound II was coupled in two consecutive steps with N^{α}-carbobenzoxy-N^{G}-tosylarginine[8] using N-ethyl-5-phenylisoxazolium-3′-sulfonate[9] for activation of the carboxyl group in both steps. The fully protected tripeptide N^{α}-carbobenzoxy-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric acid methyl ester (IV) obtained in this manner, was purified by means of extraction and countercurrent distribution in the toluene system (K = 1.04). After catalytic removal of the α-carbobenzoxy group from IV, the resulting tripeptide

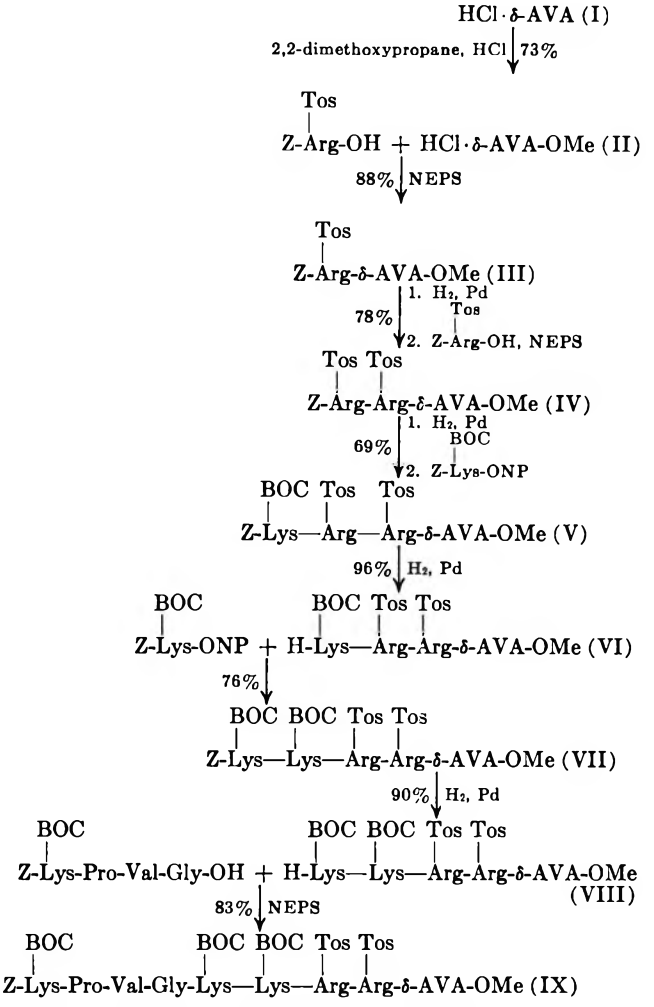

Figure 1.—Outline of the synthesis of the fully protected nonapeptide N^{α}-carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysylprolylvalylglycyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric acid methyl ester: δ-AVA, δ-aminovaleric acid; OMe, methoxy; Z, carbobenzoxy; Tos, *p*-toluenesulfonyl; NEPS, N-ethyl-5-phenylisoxazolium-3′-sulfonate; BOC, *t*-butyloxycarbonyl; ONP, *p*-nitrophenyl.

free base was coupled with N^{α}-carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysine *p*-nitrophenyl ester[10] in two subsequent steps to give the fully protected pentapeptide N^{α}-carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric acid methyl ester (VII). Peptide VII, which was obtained in amorphous form, behaved as a single component (K = 0.56) during countercurrent distribution in the toluene system and was also homogeneous by the criteria of paper and thin layer chroma-

(1) (a) This work was supported in part by a grant from the U. S. Public Health Service (GM-02907). A scholarship from the South African Department of Agriculture Technical Services received by one of us (W. O.) is greatly appreciated.

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tography in several solvent systems, both before and after removal of the carbobenzoxy group. For the condensation of the pentapeptide free base N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric acid methyl ester (VIII) with the tetrapeptide acid N^{α}-carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysylprolylvalylglycine,[11] N-ethyl-5-phenylisoxazolium-3′-sulfonate was employed once again as carboxyl activating agent to give the fully protected nonapeptide IX. Compound IX was obtained in crystalline form and was homogeneous by the criteria of countercurrent distribution and thin layer chromatography in several solvent systems.

Experimental Section[12-15]

δ-Aminovaleric Acid Methyl Ester Hydrochloride (II).—δ-Aminovaleric acid hydrochloride (I) (4.61 g, 30 mmol) was suspended in 200 ml of 2,2-dimethoxypropane, and 15 ml of concentrated HCl was added while stirring at room temperature. Stirring was continued at room temperature for a total period of 17 hr. The intensely colored solution was then evaporated *in vacuo* to produce a dark crystalline mass, which was washed with portions of ether until free of any color. The white crystalline product (5 g) revealed in paper chromatography in the BPAW system the presence of one major spot (R_f 0.67) accompanied by a trace of δ-aminovaleric acid (R_f 0.48). The product was dissolved in 40 ml of hot absolute alcohol, and, while still hot, 80 ml of ethyl acetate were added. Upon slowly being cooled to room temperature, the ester (II) separated from the solution in the form of long needles. After a few hours at room temperature, 3.65 g (73%) of crystals was obtained: mp 145–146°; R_f BAW 0.44, R_f BPAW 0.67 in paper chromatography.

Anal. Calcd for $C_6H_{14}O_2NCl$ (167.6): C, 42.90; H, 8.41; N, 8.35. Found: C, 42.93; H, 8.60; N, 8.13.

N^{α}-Carbobenzoxy-N^{G}-tosylarginyl-δ-aminovaleric Acid Methyl Ester (III).—N^{α}-Carbobenzoxy-N^{G}-toslyarginine[8] (6.01 g, 13 mmol) was dissolved with slight warming in 130 ml of acetonitrile. After the solution was cooled in an ice bath, 1.82 ml (13 mmol) of triethylamine, followed by 3.63 g (14.3 mmol) of N-ethyl-5-phenylisoxazolium-3′-sulfonate (Woodward reagent K),[9] was added while stirring. The mixture was stirred for 1.5 hr at 0°, and then 2.18 g (13 mmol) of compound II, followed by another 1.82 ml of triethylamine, was added. Stirring was continued for another 6 hr in the cold before the temperature of the bath was allowed to increase to room temperature. After a total reaction period of 23 hr, the solvent was removed *in vacuo*, and the resulting syrup was dissolved in 200 ml of moist ethyl acetate. The solution was extracted twice with 80-ml portions of water, followed by successive extractions with similar portions of 0.1 *N* HCl, water, 5% $NaHCO_3$ solution, water, and saturated NaCl solution. After the solution was dried over anhydrous Na_2SO_4, the ethyl acetate was removed *in vacuo* and the product was dried over P_2O_5 to give 6.57 g (88%) of a glassy material: mp 40–45°; $[\alpha]^{25}D$ −1.72° (*c* 4, methanol). The product was homogeneous in paper chromatography in four systems (R_f BAW 0.84, R_f SBA 0.86, R_f BPAW 0.82, R_f nBA 0.81) as well as in four thin layer systems[16] [R_f BAW 0.70, R_f SBA 0.64, R_f BPAW 0.75, R_f CM (8:2) 0.71].

Anal. Calcd for $C_{27}H_{37}O_7N_5S$ (575.7): C, 56.32; H, 6.48; N, 12.16; S, 5.57. Found: C, 56.08; H, 6.28; N, 12.15; S, 5.72.

N^{α}-Carbobenzoxy-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric Acid Methyl Ester (IV).—A solution of the protected dipeptide (III) (3.0 g, 5.2 mmol) in absolute methanol (60 ml) was hydrogenolyzed for 5 hr in the presence of a Pd catalyst freshly prepared from 1 g of $PdCl_2$. The resulting solution was immediately investigated by means of thin layer and paper chromatography, which revealed the presence of a single ninhydrin-positive component in several systems (R_f BAW 0.28, R_f SBA 0.31, R_f CM 0.22 in thin layer chromatography, and R_f BAW 0.60, R_f SBA 0.68, R_f BPAW 0.67 on paper). As soon as it was evident from the CM thin layer system that the hydrogenolysis reaction was complete, the catalyst was removed by filtration and the methanol removed *in vacuo*.

A solution of the resulting syrup in 15 ml of acetonitrile was added without delay[17] to a mixture which was prepared in the following manner. N^{α}-Carbobenzoxy-N^{G}-tosylarginine[8] (2.41 g, 5.2 mmol) was dissolved in 35 ml of acetonitrile; triethylamine (0.73 ml, 5.2 mmol) was added, followed by 1.453 g (5.72 mmol) of Woodward reagent K[9] at 0°, and the solution was stirred in the cold for 1.5 hr. After addition of the hydrogenolysis product, stirring was continued for another hour at 0° and then for 24 hr at room temperature.

At the end of the reaction period, the mixture so obtained was evaporated *in vacuo* to a syrup, the latter was dissolved in 200 ml of moist ethyl acetate, and the solution was extracted twice with 80-ml portions of water and then with portions (80 cc) of 0.1 *N* HCl, water, 5% $NaHCO_3$ solution, water, and saturated NaCl solutions.[18] After the solution was dried over anhydrous Na_2SO_4, the solvent was removed *in vacuo;* the thoroughly dried product was dissolved in methanol (15 ml) and precipitated from anhydrous ether (600 ml). The precipitate (3.9 g) was subjected to countercurrent distribution for 100 transfers in the toluene system. From the peak obtained (K = 1.04), 3.59 g (78%) of compound IV was recovered: mp 87–91°; $[\alpha]^{24}D$ −6.22° (*c* 3, methanol), Peptide IV was homogeneous in paper chromatography in three solvents (R_f BAW 0.88, R_f SBA 0.85, R_f BPAW 0.91) as well as in three thin layer systems [R_f BAW 0.66, R_f SBA 0.63, R_f CM (8:2) 0.65].

Anal. Calcd for $C_{60}H_{55}O_{10}N_9S_2$ (886.0): C, 54.30; H, 6.26; N, 14.23; S, 7.24. Found: C, 54.20; H, 6.01; N, 14.50; S, 7.15.

(11) C. H. Li, D. Chung, and J. Ramachandran, *J. Amer. Chem. Soc.*, **86**, 2715 (1964).

(12) Melting points were determined in a Fischer-Johns melting block apparatus and are uncorrected. Microanalyses were performed in the Microanalytical Laboratory of the Department of Chemistry, University of California at Berkeley. Samples for microanalyses were dried for *ca.* 16 hr in an Abderhalden drying pistol with P_2O_5 under reduced pressure at 77 or 40° depending on the melting point of a particular sample. For paper chromatography the descending method on Whatman No. 1 filter paper was used. The solvents employed were 1-butanol–acetic acid–water (BAW) in a ratio of 4:1:1, 1-butanol–pyridine–acetic acid–water (BPAW) in a ratio of 30:20:6:24, 2-butanol–10% aqueous ammonia (SBA) in a ratio of 85:15, and 1-butanol saturated with 0.1% aqueous ammonia (nBA), using the lower phase for saturation of the atmosphere in the tank and the upper phase for the development of chromatograms. Thin layer chromatography was carried out according to the procedure of Stahl.[13] The plates were prepared by mixing 30 g of silica gel G with 100 mg each of luminescent zinc cadmium sulfide and zinc orthosilicate (Du Pont) in 65 ml of water for 30 sec at high speed in a Waring Blendor, and pouring the resulting suspension as a uniform layer (250 μ thick) on glass plates (20 × 5 cm) by means of an adjustable applicator (Desaga/Brinkmann Instrument Co., Inc., N. Y.). After 1 hr at room temperature the plates were kept at 100° for 1 hr and stored over anhydrous $CaSO_4$ ("Drierite"). In addition to the BAW, BPAW, and SBA solvent systems used in paper chromatography a system consisting of chloroform–methanol mixed in a ratio of 8:2 (CM), was also employed for development of thin layer plates; thin layer chromatograms were revealed by means of the ninhydrin reagent and the chlorine procedure,[14] and also by means of ultraviolet fluorescence quenching on thin layer plates. Hydrogenolytic operations were performed in the presence of an excess of Pd catalyst prepared freshly[15] from $PdCl_2$. A vibro-mixer (Model E1, A. G. Fuer Chemie Apparatebau, Zurich) was employed for mixing and the progress of the reaction was followed by testing for CO_2 in the outlet gas stream. The toluene system (chloroform–toluene–methanol–water mixed in a ratio of 5:5:8:2), was employed for countercurrent distribution and the distribution patterns were determined from the dry weight of material present in aliquots taken at regular intervals over the length of the distribution train.

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(15) R. Wilstätter and E. Waldschmidt-Leitz, *Chem. Ber.*, **54**, 128 (1921).

(16) During a repetition of this synthesis, the CM thin layer system revealed the presence of a trace of slower moving, ninhydrin-negative, chlorine-positive material. This contaminant could be separated from the material in the main peak (K = 0.82) during a 100-transfer countercurrent distribution in the toluene system.

(17) During preliminary experiments it was observed that, when chromatographed immediately after the completion of hydrogenolysis, the dipeptide free base behaved as a single ninhydrin-positive component in paper and thin layer systems. When the solution obtained after hydrogenolysis was stored at 0°, however, the appearance of 2 minor, faster moving ninhydrin-positive spots was noted after thin layer chromatography in the CM system and in particular in the SBA system, whereas the appearance of faster moving ninhydrin-negative material became evident in paper chromatography in the BAW and BPAW systems. The identity of these materials is not known at present.

(18) Extraction with saturated NaCl solution reduced the solubility of the peptide in the organic phase, leading to some precipitation of the product. This could be avoided by the addition of a few milliliters of methanol after extracting with the saturated NaCl solution.

N^{α}-Carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric Acid Methyl Ester (V).—Peptide IV (3.52 g, 3.97 mmol) was dissolved in absolute methanol (130 ml) and hydrogenolyzed for 4.5 hr in the presence of Pd catalyst prepared freshly from 1.5 of $PdCl_2$. The hydrogenolysis mixture was subjected immediately to thin layer chromatography, which revealed the presence of a single ninhydrin-positive spot in three solvent systems (R_f BAW 0.23, R_f SBA 0.22, R_f CM (8:2) 0.14). Paper chromatography in three solvents also revealed the presence of a single component, (R_f BAW 0.67, R_f SBA 0.70, R_f BPAW 0.37). As soon as completion of the hydrogenolysis reaction was verified by thin layer chromatography in the CM (8:2) system, the catalyst was removed by filtration and the solution was evaporated to dryness *in vacuo*. The product was dissolved directly in a mixture of dimethylformamide (2 ml) and acetonitrile (14 ml), and, while stirring at room temperature, N^{α}-carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysine *p*-nitrophenyl ester[10] (2.2 g, 4.38 mmol) was added. After 48 hr at room temperature, the reaction mixture was precipitated from anhydrous ether, and the precipitate (3.76 g) subjected to a 140 transfer countercurrent distribution in the toluene system. The material recovered from the peak (K = 0.69) was dissolved in 150 ml of chloroform, and the solution extracted successively with 50-ml portions of first a 10% citric acid solution followed by water and then with a 5% $NaHCO_3$ solution until the final aqueous phase was colorless (four extractions). After the solution was extracted once with water and then with saturated NaCl solution, the organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The glassy product (3.37 g) was dissolved in methanol and precipitated from anhydrous ether (700 ml). A solution of the precipitate in 200 ml of moist ethyl acetate was extracted once more with 50 ml of 5% $NaHCO_3$ solution and then thrice with 100-ml portions of water. The organic phase was evaporated *in vacuo* and yielded after drying over P_2O_5 3.06 g (69%) of a colorless glassy product: mp 82–85°, $[\alpha]^{23}D$ −11.2° (*c* 2, methanol), homogeneous in paper chromatography in two solvents (R_f BAW 0.84, R_f BPAW 0.86) as well as in thin layer chromatography in three solvent systems [R_f BAW 0.68, R_f SBA 0.65, R_f CM (8:2) 0.61].

Anal. Calcd for $C_{51}H_{75}O_{13}N_{11}S_2$ (1114.3): C, 55.00; H, 6.79; N, 13.84; S, 5.76. Found: C, 54.83; H, 6.87; N, 13.85; S, 5.57.

N^{ϵ}-*t*-Butyloxycarbonyllysyl-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric Acid Methyl Ester (VI).—Protected tetrapeptide (V) (2.26 g, 2.03 mmol) was dissolved in 100 ml of absolute methanol and hydrogenolyzed catalytically for 4 hr in the presence of Pd freshly prepared from 1 g of $PdCl_2$. The catalyst was removed by filtration and the solvent was evaporated *in vacuo* to yield 1.925 g (96%) of compound VI in the form of a glassy product which was homogeneous in paper chromatography in two solvents (R_f BAW 0.77, R_f BPAW, 0.89) as well as in three thin layer systems [R_f BAW 0.41, R_f BPAW 0.66, R_f CM (8:2) 0.25].

The product, after countercurrent distribution for 101 transfers in the toluene system, was distributed as a single peak (K = 2.06), $[\alpha]^{25}D$ −5.02° (*c* 1.8, methanol).

Anal. Calcd for $C_{43}H_{69}O_{11}N_{11}S_2$ (980.2): C, 52.67; H, 7.10; N, 15.72. Found: C, 52.40; H, 7.10; N, 15.60.

N^{α}-Carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric Acid Methyl Ester (VII).—To a solution of 1.47 g (1.5 mmol) of tetrapeptide free base VI in 7 ml of acetonitrile, was added 0.83 g (1.65 mmol) of N^{α}-carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysine *p*-nitrophenyl ester.[10] The mixture was stirred until a clear solution was obtained and was then allowed to stand at room temperature for 72 hr. The entire reaction mixture was precipitated from anhydrous ether (500 ml) and the yellowish precipitate (1.84 g) was subjected to countercurrent distribution in the toluene system for 150 transfers. The material recovered from the peak (K = 0.56) was dissolved in 15 ml of methanol and precipitated from anhydrous ether (600 ml) to give 1.53 g (76%) of peptide VII in the form of a white amorphous powder, mp 83–88°, $[\alpha]^{26}D$ −14.3° (*c* 1.5, methanol). The product behaved as a single component in three paper chromatographic systems (R_f BAW 0.90, R_f SBA 0.88, R_f BPAW 0.92) and was homogeneous in thin layer chromatography in four solvent systems [R_f BAW 0.72, R_f SBA 0.66, R_f BPAW 0.69, R_f CM (8:2) 0.64].

Anal. Calcd for $C_{62}H_{95}O_{16}N_{13}S_2$ (1342.6): C, 55.46; H, 7.13; N, 13.56; S, 4.77. Found: C, 55.21; H, 7.20; N, 13.51; S, 4.66.

N^{ϵ}-*t*-Butyloxycarbonyllysyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric Acid Methyl Ester (VIII).—A solution of 0.8 g (0.6 mmol) of the fully protected pentapeptide (VII) in 40 ml of methanol was hydrogenolyzed for 4 hr in the presence of a Pd catalyst prepared from 0.5 g of $PdCl_2$. After the suspension was kept at 0° overnight, the catalyst was removed by filtration, the solution concentrated to a small volume *in vacuo* at room temperature and the product precipitated from anhydrous ether to give 0.65 g (90%) of the free base VIII as an amorphous powder: mp 95–100°; $[\alpha]^{23}D$ −9.6° (*c* 1, methanol). Peptide VIII behaved as a single component in paper chromatography in two solvents (R_f BAW 0.87, R_f SBA 0.93) as well as in thin layer chromatography in three solvent systems [R_f BAW 0.53, R_f SBA 0.45, R_f CM (8:2) 0.34].

Anal. Calcd for $C_{54}H_{89}O_{14}N_{13}S_2$ (1208.5): C, 53.70; H, 7.42; N, 15.05. Found: C, 53.36; H, 7.47; N, 14.89.

N^{α}-Carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysylpropylvalylglycyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{ϵ}-*t*-butyloxycarbonyllysyl-N^{G}-tosylarginyl-N^{G}-tosylarginyl-δ-aminovaleric Acid Methyl Ester (IX).—N^{α}-Carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyllysylpropylvalylglycine[11] (0.323 g, 0.508 mmol) was dissolved in 6 ml of acetonitrile with slight warming. While the solution was cooled at 0°, 0.072 ml (0.51 mmol) of triethylamine followed by 0.143 g (0.56 mmol) of Woodward reagent K[9] was added and the mixture was kept stirring at 0° for 1.5 hr. A solution of VIII (0.614 g, 0.508 mmol) in 10 ml of acetonitrile was added and stirring were continued at room temperature for 18 hr. Substantial amounts of crystalline material, which started to separate from the reaction mixture several minutes after the addition of VIII, were filtered off at the end of the reaction period after the mixture was left for a few hours at 0°. After the crystalline fraction was washed with some ice-cold acetonitrile, followed by ethyl ether, it was dried *in vacuo* over P_2O_5. The washing solvents and the mother liquor fraction were combined and evaporated to dryness and the resulting yellow syrup was dissolved in 70 ml of chloroform. The solution was extracted successively with 40-ml portions of water, a 10% citric acid solution, followed by water, and a saturated NaCl solution. The organic phase was dried over anhydrous Na_2SO_4 and yielded 0.174 g of material after removal of the solvent. The latter fraction was contaminated with three minor slower moving chlorine-positive components as revealed by thin layer chromatography in the CM system, and was purified by means of countercurrent distribution for 100 transfers in the toluene system. The material recovered after countercurrent distribution was combined with the crystalline fraction (0.7 g) originally obtained and subjected to another 100 transfer distribution in the toluene system. A single peak (K = 0.34) which closely approached the theoretical distribution pattern, was obtained and yielded 0.83 g of material which was dissolved in a small volume of methanol (1–2 ml) and became crystalline upon cooling and scratching. After some cold ethyl acetate was added, the crystalline product was filtered off and dried to give 0.82 g (83%) of peptide IX, mp 152–154°, $[\alpha]^{26}D$ −26.9° (*c* 1, methanol). The product was homogeneous in thin layer chromatography in four solvent systems [R_f BAW 0.67, R_f BPAW 0.73, R_f SBA 0.61, R_f CM (8:2) 0.67].

Anal. Calcd for $C_{85}H_{134}O_{22}N_{18}S_2$ (1824.2): C, 55.97; H, 7.40; N, 13.82; S, 3.51. Found: C, 55.62; H, 7.69; N, 14.08; S, 3.66.

Registry No.—II, 15764-82-6; III, 15764-83-7; IV, 15889-52-8; V, 15764-99-5; VI, 15764-84-8; VII, 15815-82-4; VIII, 15764-85-9; IX, 15889-53-9.

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Preparation of Sugar Phosphates by Displacement of Primary Sulfonyloxy Groups

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A primary *p*-tolylsulfonyl group in certain otherwise acetylated sugars and glycosides can be displaced by diphenyl phosphate ion in refluxing dimethylformamide. Subsequent removal of protecting groups gives the phosphorylated sugar or glycoside. In this way D-glucose 6-phosphate was prepared in low yield and the anomeric methyl α- and β-D-glucopyranoside 6-phosphates in moderate yield (about 35%). In the last-mentioned case, methyl β-D-glucopyranoside 6-(monophenyl phosphate) was isolated as an intermediate.

The displacement of a sulfonyloxy group on primary as well as on secondary hydroxyl groups in carbohydrates has led to the formation of a variety of substituted sugars, and the versatility of this general synthetic route is continually being exploited. As yet, however, the successful introduction of phosphate groups by this method does not appear to have been described. The present report records modest success in this direction, with the displacement of a primary *p*-tolylsulfonyloxy group in otherwise acetylated derivatives of β-D-glucopyranose, methyl β-D-glucopyranoside, and methyl α-D-glucopyranoside.

The analogous preparation of phosphorylated sugars by displacement of a primary halogen has met with varying degrees of success. Silver dibenzyl phosphate has been used to prepare a derivative of uridine 5′-phosphate from 5′-deoxy-5′-iodo-2′,3′-*O*-isopropylideneuridine[2] and the same reagent has been used to prepare phosphatidic acid derivatives from diacylglycerol α-iodohydrins.[3] On the other hand, methyl 3,4-di-*O*-acetyl-2,6-dideoxy-6-iodo-α-D-glucopyranoside and methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside react only very slowly with silver diphenyl phosphate[4] at 80°. (The products of these reactions were not described.) The unacetylated compounds readily undergo reaction, but the product is not the result of a simple displacement. Thus, methyl 6-deoxy-6-iodo-α-D-glucopyranoside and methyl 2,6-dideoxy-6-iodo-α-D-glucopyranoside readily yield the corresponding 3,6-anhydro derivatives when treated with silver diphenyl phosphate.[4,5] In the work described herein, we have used the fully acetylated derivatives in order to avoid this anhydride formation, and have carried out the reactions at higher temperatures.

When a sample of 1,2,3,4-tetra-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranose was refluxed in dimethylformamide with an excess of lithium diphenyl phosphate considerable decomposition took place. The product which contained esterified phosphate[6] in a yield of 34%, was subjected to hydrogenolysis and hydrolysis and yielded D-glucose 6-phosphate as the sparingly soluble hydrated barium salt in a yield of only 3 to 4%. The other products of the reaction were not investigated. The reaction of methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside with lithium diphenyl phosphate proceeded more smoothly. The crude material, containing esterified phosphate in 58% yield, was converted into the cyclohexylammonium salt of methyl α-D-glucopyranoside 6-phosphate mp 195–205°, $[\alpha]^{20}D$ +60°, in 35% yield. Szabó and Szabó[7] reported mp 157–159° and $[\alpha]^{25}D$ +61° for their anhydrous material. In our laboratory, this compound was hydrated, whether prepared by displacement as above or by phosphorylation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside following the directions of Szabó and Szabó.[7]

In a similar manner, after the action of lithium diphenyl phosphate on methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranoside, hydrogenolysis and hydrolysis gave a crystalline cyclohexylammonium salt in 38% yield. However, this proved to be a salt of methyl β-D-glucopyranoside 6-(monophenyl phosphate). The removal of both phenyl groups is prevented presumably either by steric factors or by poisoning of the platinum catalyst. Charcoal treatment and repetitive addition of fresh catalyst did not effect the desired hydrogenolysis, suggesting that the inhibition may be steric. Furthermore, phosphorylation of methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside with diphenyl phosphorochloridate followed by hydrogenolysis led to the same phospho diester. In contrast to this behavior of the acetylated material, the purified deacetylated product readily underwent hydrogenolysis of the sole remaining phenyl group to produce methyl β-D-glucopyranoside 6-phosphate, isolated as its cyclohexylammonium salt in 87% yield.

Experimental Section

Thin layer chromatography was run on Avicel plates[8] using ethyl acetate–acetic acid–water (3:3:1) as irrigating solvent and the Hanes–Isherwood spray[9] for spot detection. The R_f values found were as follows: methyl β-D-glucopyranoside 6-(monophenyl phosphate), 0.75; methyl β-D-glucopyranoside 6-phosphate and methyl α-D-glucopyranoside 6-phosphate, 0.53; D-glucose 6-phosphate, 0.28; and inorganic phosphate, 0.60.

Lithium Diphenyl Phosphate.—Diphenyl phosphoric acid (25 g) in water (40 ml) was neutralized (pH 7) with 2 *N* lithium hydroxide and the solution was evaporated *in vacuo*. The resulting white solid was air dried and used without further purification.

D-Glucose 6-(Barium phosphate).—A mixture of 1,2,3,4-tetra-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranose[10] (4 g) and lithium diphenyl phosphate (6 g, *ca.* 3 molar equiv) in dry dimethylformamide (10 ml) was heated under reflux. The solids rapidly dissolved and after 3 hr the dark mixture was concen-

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trated at reduced pressure. The residual solids were partitioned between chloroform and water and the organic layer was washed several times with water and then dried with anhydrous sodium sulfate. The chloroform was evaporated and the residual syrup dissolved in methanol; this solution was treated with charcoal and filtered and the charcoal treatment was repeated giving after removal of solvent, a bright yellow syrup. This was dissolved in 30 ml of 95% ethanol, 2 drops of concentrated hydrochloric acid was added, and the material was hydrogenated overnight at room temperature and 45 psi using 400 mg of Adams catalyst. The catalyst was removed by centrifugation and the solution was treated with charcoal and filtered; the hydrogenation was repeated with a second portion of catalyst. To the filtered solution (75 ml), 4 ml of concentrated ammonium hydroxide was added and the solution left overnight. The solution was then concentrated *in vacuo* and the residue dissolved in water, treated batchwise with Dowex 50 H^+ (50 ml), and filtered and 1.2 g of barium acetate added. This solution was then evaporated to a small volume and seeded with authentic D-glucose 6-(barium phosphate) heptahydrate to yield 160 mg (3.8%).

Methyl β-D-Glucopyranoside 6-(Cyclohexylammonium Monophenyl Phosphate). A. By *p*-Tolylsulfonyl Displacement.—Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranoside[11] (2 g) and lithium diphenyl phosphate (3.1 g, *ca.* 3 molar equiv) were refluxed in DMF (6 ml) for 2 hr and the mixture was worked up with chloroform as described above. Dissolution of the syrup in ethyl acetate and addition of petroleum ether resulted in the recovery of 200 mg of starting glycoside. The mother liquor remaining was concentrated *in vacuo* and the residue dissolved in ethanol the solution was treated thrice with charcoal and filtered. This was then shaken overnight with hydrogen at room temperture and 3 atm of pressure in the presence of 200 mg of Adams catalyst and 2 drops of concentrated hydrochloric acid. The catalyst was removed by filtration and the hydrogenation was repeated three times, each time with fresh catalyst. Acetyl groups were then removed by addition of ammonium hydroxide and heating on a steam bath and the residue, in aqueous solution, was passed through a column of Dowex 50W H^+ and then treated with excess cyclohexylamine. The solution was evaporated and the product crystallized from water by the addition of acetone. The yield of air-dried product was 650 mg (38%): mp 228° dec, $[\alpha]^{20}D$ −21.6° (c 1, H_2O).

Anal. Calcd for $C_{19}H_{32}NO_9P$ (449.4) C, 50.77; H, 7.18; N, 3.12; P, 6.89. Found:[12] C, 50.55; H, 7.25; N, 3.16; P, 6.74.

B. By Phosphorylation with Diphenyl Phosphorochloridate Diphenyl phosphorochloridate (1.5 g) was added to dry pyridine (14 ml) containing methyl 2,3,4-tri-*O*-acetyl-β-D-glucopyranoside[13] (1.6 g) and the solution was left 2 days at room temperature. Water (2 ml) was then added and after 0.5 hr the solvent was removed *in vacuo*. The residue was dissolved in chloroform and the solution was washed with water, 1 *N* sulfuric acid, and then again with water and dried (sodium sulfate). The syrup (2.8 g) which remained after removal of solvent was dissolved in ethanol and shaken overnight with hydrogen at room temperature and 3 atm of pressure in the presence of 0.2 g of Adams catalyst. The acetyl groups were removed and the product isolated as described above to yield 500 mg (22%): mp 225°, $[\alpha]^{20}D$ −21.2° (c 1, H_2O). This material is chromatographically identical with the above-described substance.

Methyl β-D-Glucopyranoside 6-(Dicyclohexylammonium phosphate).—A 0.4-g sample of methyl β-D-glucopyranoside 6-(cyclohexylammonium monophenyl phosphate) in water was converted into the free acid using a small column of Dowex 50W H^+. The resulting solution was concentrated *in vacuo* and the residue dissolved in ethanol (30 ml) and hydrogenated overnight at room temperature and 3 atm of pressure using 200 mg of platinum oxide. The resulting filtered solution was made alkaline with cyclohexylamine and concentrated at reduced pressure and the residue was crystallized from water by the addition of acetone. The air-dried product weighed 375 mg (87%): mp 185°, $[\alpha]^{20}D$ −25.6° (c 1, H_2O)

Anal. Calcd for $C_{19}H_{41}N_2O_9P \cdot {}^1/_2H_2O$ (481.5): C, 47.39; H, 8.79; N, 5.82; P, 6.43. Found: C, 47.14; H, 8.77; N, 5.49; P, 6.24.

Methyl α-D-Glucopyranoside 6-(Dicyclohexylammonium Phosphate).—Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside[14] (0.85 g) and lithium diphenyl phosphate (1.25 g) were refluxed in dimethylformamide (9 ml) for 10 hr. The product was worked up as described in the displacement reaction on the α anomer, except that no starting material was recovered. The final air-dried product weighed 300 mg (35%) after crystallization from water–acetone, and showed mp 195–205°, $[\alpha]^{20}D$ +60° (c 1, H_2O).

The compound was also prepared by phosphorylation of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside with diphenyl phosphorochloridate following the procedure of Szabó and Szabó,[7] except that the hydrogenation was performed at 3 atm rather than 1 atm of pressure. The product was obtained in 66% yield and had melting point and rotation identical with those of the product obtained by tosyl displacement. Szabó and Szabó obtained anhydrous material with mp 157–159° and $[\alpha]^{25}D$ +61°.

Anal. Calcd for $C_{19}H_{41}N_2O_9P \cdot {}^1/_2H_2O$ (481.5) C, 47.39; H, 8.79; N, 5.82; P, 6.43. Found: C, 47.19; H, 8.80; N, 5.64; P, 6.05.

Registry No.—$C_{19}H_{32}NO_9P$, 15764-86-0; $C_{19}H_{41}N_2O_9P$ (β-D), 15764-87-1; $C_{19}H_{41}N_2O_9P$(α-D), 15764-88-2.

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4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-D-talopyranose Hydrochloride[1,2]

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Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (1) was converted into methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranosid-4-ulose (2) *via* a dimethyl sulfoxide–phosphorus pentoxide oxidation. Reaction of the 4-ketose derivative with hydroxylamine hydrochloride followed by lithium aluminum hydride reduction and *N*-acetylation afforded methyl 4-acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (9) in high yield. The reduction was stereospecific since less than 2% of the C-4 epimer having the *manno* configuration could be isolated. The major isomer was converted into a number of *N*-substituted derivatives including the crystalline α and β isomers of the title compound, 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-D-talopyranose hydrochloride (23 and 24). Molecular rotations, nmr spectra, mixture melting point determinations, mass spectral data, X-ray crystallographic data, and degradation studies unambiguously confirm the assigned structures.

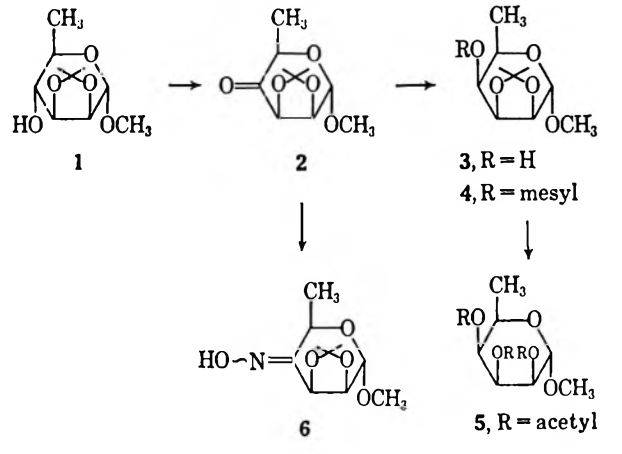
A rearrangement of 6-deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-mannopyranoside and related sulfonate esters recently was discovered in our laboratory. Under conditions expected to give normal displacement products with a variety of nucleophiles the sulfonate ester yielded ring-contracted products.[3-5] Accordingly, other routes to the D-*talo*, as well as the D-*manno* configurations were sought. One such reaction sequence involves the preparation of a suitably protected 4-oximino derivative of a hexos-4-ulose which could then be reduced to one or both of the 4-amino sugars having the D-*talo* and D-*manno* configurations depending on the stereochemistry of the reduction step. The synthesis of these potentially biologically interesting 4-amino-4,6-dideoxy sugar derivatives[6] forms the basis of this paper.[7]

Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (1), readily available from our earlier work,[3] served as the starting material for the preparation of ketone 2. The oxidation of the enantiomer of compound 1 had been reported earlier by Collins and Overend[8,9] using chromium trioxide–pyridine. Also, the crystalline triacetate 5 was described.[8,9] Recently, Jones, *et al.*,[10] have reported the same conversion using ruthenium tetroxide. In our hands, the chromium trioxide–pyridine reaction of Collins and Overend was time consuming, requiring five successive treatments to give a 30% yield of 91% pure 4-keto derivative 2.

A modification of a recently reported phosphorus pentoxide–dimethyl sulfoxide procedure[11] was evaluated and gave good results. Thus compound 1 was oxidized smoothly with phosphorus pentoxide in a dimethyl sulfoxide–pyridine mixture to yield ketone 2 (96% purity by vpc analysis) in 81% yield (Scheme I), identical with the product obtained from the reported chromium trioxide oxidation. Compound 2 was reduced stereoselectively by sodium borohydride in methanol to yield 3, the C-4 epimer of compound 1, in 85% yield. The *talo* derivative 3 (90% purity) was contaminated with 2% of 1 and 8% of an unknown impurity. Compound 3 was converted into the crystalline triacetate 5 in 53% over-all yield by selective hydrolysis of the 2,3-*O*-isopropylidene bridge followed by acetylation with acetic anhydride in pyridine. The physical constants of triacetate 5 were in agreement with those reported for its enantiomer.[8,9] Compound 3 was also converted into its crystalline mesylate 4 in 73% yield by mesylation in pyridine. With these results in hand, ketone 2 was converted into its crystalline oxime derivative 6 in 64% yield. The nmr spectrum of the oxime (Figure 1) is in agreement with the proposed structure. The oxime 6 was reduced with

SCHEME I

PREPARATION OF DERIVATIVES OF METHYL 6-DEOXY-2,3-*O*-ISOPROPYLIDENE-α-D-*lyxo*-PYRANOSID-4-ULOSE (2)



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(6) (a) C. L. Stevens, P. Blumbergs, F. A. Daniher, J. Strominger, M. Matsuhashi, D. Dietzler, S. Suzuki, T. Okazaki, K. Sugimoto, and R. Okazaki, *J. Amer. Chem. Soc.*, **86**, 2939 (1964); (b) C. L. Stevens, P. Blumbergs, and F. A. Daniher, *ibid.*, **85**, 1552 (1963); (c) R. W. Wheat, E. L. Rollins, and J. M. Leatherwood, *Biochem. Biophys. Res. Commun.*, **9**, 120 (1962); (d) C. L. Stevens, P. Blumbergs, D. Otterbach, J. Strominger, M. Matsuhashi, and D. Dietzler, *J. Amer. Chem. Soc.*, **86**, 2937 (1964); (e) C.-H. Lee and C. P. Schaffner, *Tetrahedron Lett.*, 5837 (1966); (f) C. L. Stevens, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, Abstract D23. This reference described the importance of 4-amino-4,6-dideoxy sugars in biological systems as well as an improved method of degradation of 4-acetamido-4,6-dideoxy sugars to D- and L-threoninol and D- and L-allothreoninol oxalates. More detailed results will be published elsewhere.

(7) Dr. J. Jarý has indicated in a private communication and he and his co-workers have successfully prepared derivatives of methyl 4-amino-4,6-dideoxy-L-talopyranoside by a different route. NOTE ADDED IN PROOF.— This work has since appeared [J. Jarý, P. Novak, Z. Ksandr, and Z. Samek, *Chem. Ind.* (London), 1490 (1967)]; also *cf.* S. W. Gunner, W. G. Overend, and N. R. Williams, *Carbohyd. Res.*, **4**, 498 (1967).

(8) P. M. Collins and W. G. Overend, *Chem. Ind.* (London), 374 (1963).

(9) P. M. Collins and W. G. Overend, *J. Chem. Soc.*, 1912 (1965).

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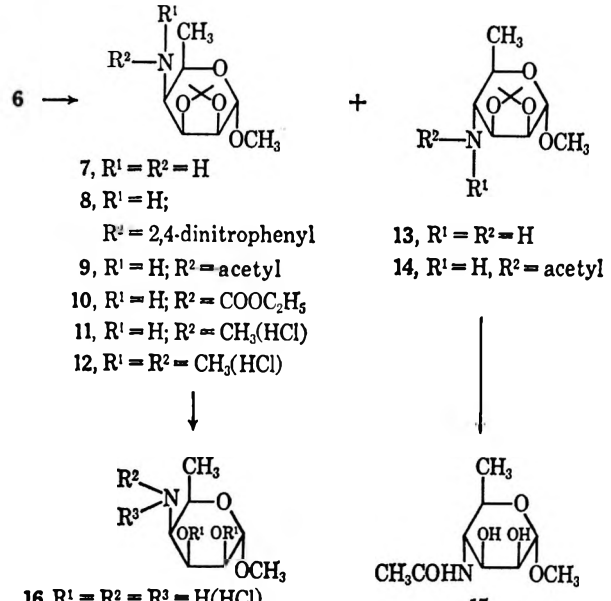
(11) K. Onodera, S. Kirano, and N. Kashimura, *J. Amer. Chem. Soc.*, **87**, 4651 (1965).

excess lithium aluminum hydride in refluxing tetrahydrofuran to afford, in 95% yield, methyl 4-amino-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**) as an oil containing a small amount of the D-*manno* isomer **13** (Scheme II). The crude mixture was converted into

SCHEME II

METHYL 4-ACETAMIDO-4,6-DIDEOXY-α-D-MANNOPYRANOSIDE (**14**), METHYL 4-AMINO-4,6-DIDEOXY-α-D-TALOPYRANOSIDE HYDROCHLORIDE (**16**), AND DERIVATIVES



7, $R^1 = R^2 = H$
8, $R^1 = H$; R^2 = 2,4-dinitrophenyl
9, $R^1 = H$; R^2 = acetyl
10, $R^1 = H$; $R^2 = COOC_2H_5$
11, $R^1 = H$; $R^2 = CH_3(HCl)$
12, $R^1 = R^2 = CH_3(HCl)$
13, $R^1 = R^2 = H$
14, $R^1 = H$, R^2 = acetyl
15
16, $R^1 = R^2 = R^3 = H(HCl)$
17, $R^1 = R^2 = H$; R^3 = acetyl
18, $R^1 = R^2$ = acetyl; $R^3 = H$
19, $R^1 = H$; $R^2 = R^3 = CH_3$(picric acid)
20, $R^1 = H$; $R^2 = R^3 = CH_3(CH_3I)$
21, R^1 = acetyl; $R^2 = R^3 = CH_3$
22, R^1 = acetyl; $R^2 = R^3 = CH_3(HCl)$

the *N*-acetyl derivatives **9** and **14**. By crystallization, pure D-*talo*-4-acetamido derivative **9** was obtained in 66% yield. The mother liquor was subjected to preparative thin layer chromatography to yield an additional 5% of the D-*talo* compound **9**, as well as 1.3% of a new *N*-acetyl derivative **14** having an infrared spectrum (chloroform) very similar to that of compound **9**. The configuration of this component **14** was established as D-*manno;* selective hydrolysis of the 2,3-*O*-isopropylidene protecting group yielded methyl 4-acetamido-4,6-dideoxy-α-D-mannopyranoside (**15**). A mixture melting point of this product with compound **15** obtained by another route,[6f] similar to that reported by Jarý, Čapek, and Kovář,[12] was undepressed and the infrared spectra of both compounds were identical. Crude amine **7** was converted into the crystalline 4-(2,4-dinitroanilino) derivative **8** in 67% yield by the method of Lloyd and Stacey.[13]

Selective hydrolysis of the 2,3-*O*-isopropylidene group of crude **7** and the *N*-acetyl derivative **9** with dilute aqueous hydrochloric acid afforded methyl 4-amino-4,6-dideoxy-α-D-talopyranoside hydrochloride (**16**) in 63% yield and methyl 4-acetamido-4,6-dideoxy-α-D-talopyranoside (**17**) in 59% yield. A mixture melting point of compound **17** with methyl 4-acetamido-4,6-dideoxy-α-D-mannopyranoside (**15**) was

(12) J. Jarý, K. Čapek, and J. Kovář, *Collect. Czech. Chem. Commun.*, **28**, 2171 (1963).
(13) P. F. Lloyd and M. Stacey, *Tetrahedron*, **9**, 116 (1960).

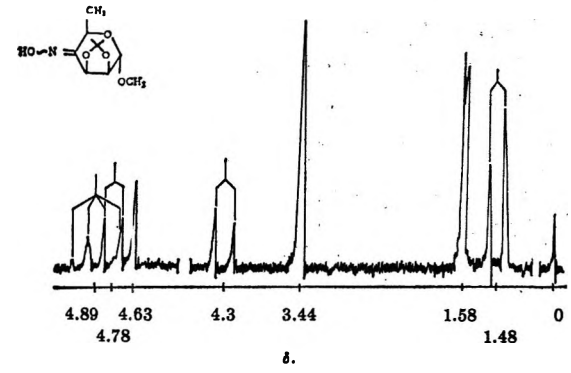


Figure 1—Nmr spectrum of methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranosid-4-ulose oxime (**6**).

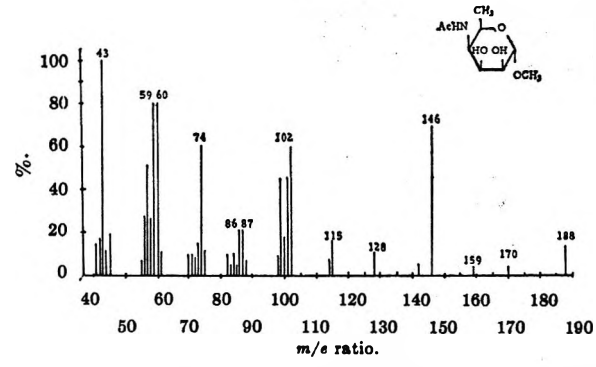


Figure 2—Mass spectrum of methyl 4-acetamido-4,6-dideoxy-α-D-talopyranoside (**17**).

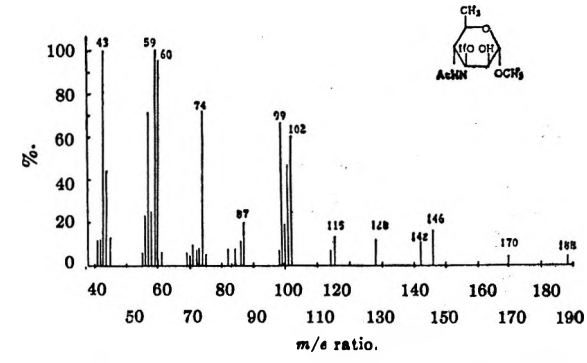


Figure. 3.—Mass spectrum of methyl 4-acetamido-4,6-dideoxy-α-D-mannopyranoside (**15**).

depressed 30°. The mass spectrum of compound **17** was identical with that of compound **15**[6f] (and certain other 4-acetamido sugars available in this laboratory) except for minor variations in peak intensity (Figures 2 and 3).

Acetylation of the free base of compound **16** in acetic anhydride and pyridine gave triacetate **18**. The same triacetate **18** was obtained from methyl 4-acetamido-4,6-dideoxy-α-D-talopyranoside (**17**), which in turn had been prepared from 2,3-*O*-isopropylidene protected *N*-acetyl derivative **9** by selective acid hydrolysis. The nmr spectrum of triacetate **18** is shown in Figure 4 and the mass spectral comparison with the triacetate obtained from *manno* derivative **15**[6f] is shown in Figures 5 and 6. Again the similarities of the mass spectra are striking. Assignments of the various protons in the nmr spectrum are given in the Experimental Section.

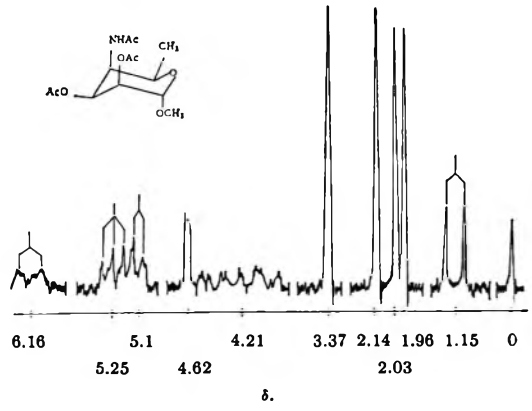


Figure 4.—Nmr spectrum of methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-talopyranoside (18).

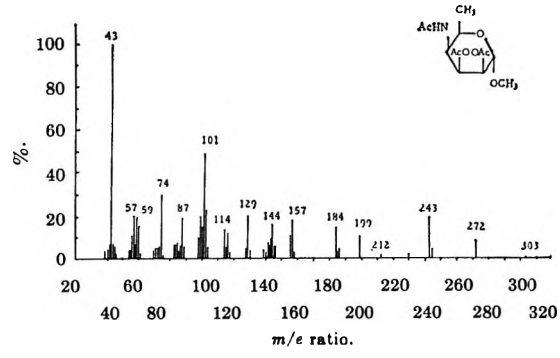


Figure 5.—Mass spectrum of methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-talopyranoside (18).

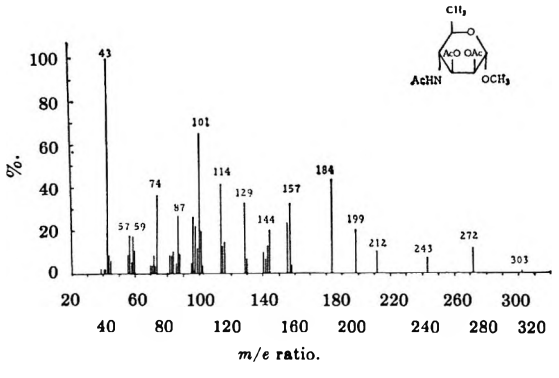


Figure 6.—Mass spectrum of methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-mannopyranoside.

Further support for the D-*talo* configuration of these amino sugar derivatives is given by a comparison of the molecular rotations of compounds **5**, **16**, **17**, **23**, and **24** with similar compounds of known D-*talo* configuration (Table I). In general, the molecular rotation of pyranose derivatives is not substantially affected by replacement of a hydroxyl by an amino group.[14-17] However, a correction factor of −3000° should be applied to the molecular rotation of an α- or β-D-hexose for comparison with the molecular rotation of a 6-deoxy-α- or β-hexose owing to the asymmetrical rotation of the 5,6-exocyclic bond, which does not contribute to the rotation of the 6-deoxyhexoses; a correction factor of +3000° should be applied also to L-hexoses.[18,19] This correction factor has been applied to the values quoted in Table I and in subsequent comparisons. The triacetates **5** and **18**, the glycoside

TABLE I
MOLECULAR ROTATION COMPARISONS OF VARIOUS AMINO SUGARS

	[α]D, deg	[M]D, deg
Methyl 4-acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-talopyranoside (18)	+82 (chloroform) +67.8 (methanol)	+24,800 +20,600
Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-talopyranoside (5)	+76 (methanol)	+23,100
Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-talopyranoside[c,d]	+73.3 (methanol) +75.9 (methanol)	+22,400[a] +23,100[a]
Methyl 3-acetamido-2,4-di-*O*-acetyl-3,6-dideoxy-α-D-talopyranoside[e]	+72 (chloroform)	+21,800
Methyl 4-amino-4,6-dideoxy-α-D-talopyranoside hydrochoride (16)	+99.3 (water)	+21,200
Methyl 6-deoxy-α-D-talopyranoside[c,d]	+104 (water) +102 (water) +106 (water)	+18,600[a] +18,200[a] +18,900[a]
Methyl 3-amino-3-deoxy-α-D-talopyranoside hydrochloride[f]	+90 (water)	+20,600 +17,600[b]
Methyl 2-amino-2,6-dideoxy-α-D-talopyranoside hydrochloride[c,g]	+84 (water)	+17,900[a]
Methyl 3-amino-3-deoxy-β-L-allopyranoside[h]	+54 (water)	+9,650 +6,650[b]
Methyl β-L-allopyranoside[i,l]	... (water)	+10,900 +7,900[b]
Methyl β-L-gulopyranoside[i,l]	+83.3 (water)	+16,200 +13,200[b]
Methyl 4-acetamido-4,6-dideoxy-α-D-talopyranoside (17)	+139.5 (water)	+30,600
Methyl 3-acetamido-3,6-dideoxy-α-D-talopyranoside[e]	+104 (water)	+22,800
4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranose hydrochloride (24)	+35 (water)	+7,250
α-D-Talose[i,l]	+68 (water)	+12,200 +9,200[b]
3-Amino-3,6-dideoxy-α-D-talose hydrochloride[e]	+41 (water)	+8,200
3-Amino-3-deoxy-α-D-talose hydrochloride[f]	+29.5 (water)	+9,300 +6,300[b]
α-L-Gulose[i,l]	... (water)	−11,500 −8,500[b]
4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-β-D-talopyranose hydrochloride (23)	+11.5 (water)	+2,600
β-D-Talose[i,l]	+13.2 (water)	+2,380 −720[b]
6-Deoxy-β-L-allose[i,k]	... (water)	+2,000

[a] These values have been obtained from those quoted for the opposite (D or L) enantiomers. [b] A correction factor[14,18,19] of −3000° has been applied to the D sugars and +3000° to the L sugars. [c] See ref 8. [d] See ref 9. [e] See ref 14. [f] H. H. Baer, *J. Amer. Chem. Soc.*, **84**, 83 (1962). [g] P. M. Collins and W. G. Overend, *J. Chem. Soc.*, 3448 (1965). [h] B. Lindberg and O. Theander, *Acta Chem. Scand.*, **13**, 1226 (1959). [i] P. A. Levene and J. Compton, *J. Biol. Chem.*, **116**, 169 (1936). [j] F. J. Bates, "Polarimetry, Saccharimetry and the Sugars," U. S. Government Printing Office, Washington, D. C., 1942. [k] F. Micheel, *Chem. Ber.* **63**, 347 (1930). [l] See ref 18.

(14) A. C. Richardson and K. A. McLauchlan, *J. Chem. Soc.*, 2499 (1962).
(15) H. Ogawa, T. Ito, S. Kondo, and S. Inoue, *Bull. Agr. Chem. Soc. Japan*, **23**, 289 (1959).
(16) A. C. Richardson and H. O. L. Fisher, *J. Amer. Chem. Soc.*, **83**, 1132 (1961).
(17) E. E. van Tamelen, J. R. Dyer, H. E. Carter, J. V. Pierce, and E. E. Daniels, *ibid.*, **78**, 4817 (1956).
(18) D. H. Whiffen, *Chem. Ind.* (London), 964 (1956).
(19) J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5483 (1959).

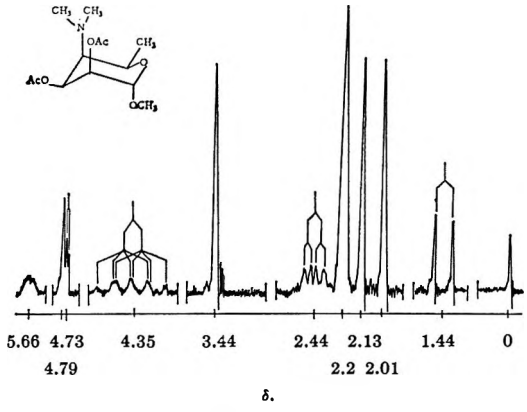


Figure 7.—Nmr spectrum of methyl 2,3-di-*O*-acetyl-4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside (**21**).

16, and the free sugars **23** and **24** compare very favorably with similar *talo* derivatives. There is a discrepancy in the comparison of *N*-acetyl derivative **17** with methyl 3-acetamido-3,6-dideoxy-α-D-talopyranoside. However, a similar difference in molecular rotation between various acetamido derivatives of glucose has been noted.[14] The molecular rotation of the β-D-free sugar **23** (+2600°), which compares favorably with β-D-talose (−720°), cannot be distinguished from 6-deoxy-β-L-allose (+2000°). However, the molecular rotation of the 4-aminoglycoside **16** (+21,200°) is very different from values for methyl β-L-allopyranoside derivatives (+6650, +7900°), but is in agreement with various methyl α-D-talopyranoside derivatives (+17,600 to +18,900°). Similarly the 4-aminoglycoside **16** (+21,200°) can be distinguished from β-L-gulopyranoside derivatives (+13,200°). Also, the molecular rotation of the α-D-free sugar **24** (+7250°) agrees with the values for α-D-talo derivatives (+6300 to +9200°) but not at all with α-L-gulose (−8500°). Derivatives of either or both of these L sugars could have resulted from epimerization of C-6 of ketone **2** during oxime formation, before reduction with lithium aluminum hydride. This possibility was eliminated by degradation of *N*-acetyl derivative **17** to L-threoninol oxalate,[6f] identical in all respects with an authentic sample prepared from L-threonine.[5f]

Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**) was converted into the *N*-methylamino hydrochloride derivative **11** by sequential *N*-carboethoxylation, lithium aluminum hydride reduction, and hydrochloride salt formation in an over-all yield of 76%. Furthermore, compound **7** also gave the *N*,*N*-dimethylamino derivative **12** in 75% yield by reductive methylation followed by conversion into the hydrochloride salt. The isopropylidene protecting group of compound **12** was selectively hydrolyzed to yield methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside. The latter compound was transformed into the crystalline picrate **19**, methiodide **20**, and diacetate **21**. The yields of picrate **19**, methiodide **20**, and diacetate **21** from starting material **12** were 94, 65, and 54%, respectively. Diacetate **21** also formed a crystalline hydrochloride **22**. The nmr spectrum of diacetate **21** is shown in Figure 7 and further details are given in the Experimental Section. *N*,*N*-Dimethylamino derivative **12**

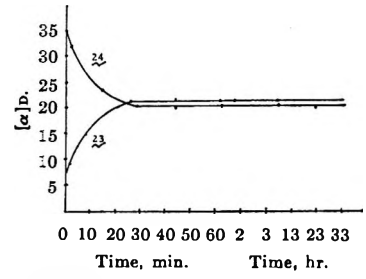
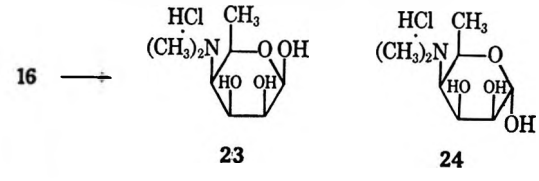


Figure 8.—Mutarotation curves of compounds **23** and **24**.

was treated with 1.0 *N* hydrochloride acid at 95° for 20 hr to give a 96% yield of crude free α- and β-D sugars **24** and **23**. The α anomer **24** was obtained as a residue by extraction of the mixture of α and β anomers with small portions of hot absolute ethanol which removed the more soluble β anomer. The β anomer **23** could be obtained relatively free of the α anomer by slow, careful crystallization from a methanol–ethyl ether mixture. The assignment of α and β configurations (Scheme III) is based on the

SCHEME III
4,6-DIDEOXY-4-(*N*,*N*-DIMETHYLAMINO)-α- AND -β-D-TALOPYRANOSE HYDROCHLORIDE.



mutarotation behavior of the two anomers which is represented in Figure 8. The pK_a of β anomer **23** (8.22) is quite high relative to that of the α anomer **24** (7.60). Attempts presently are being made in this laboratory to relate pK_a to conformation through various analytical tools (nmr, X-ray crystallography, etc.), an area that is currently little understood. As a preliminary step to this goal, the structure of methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside methiodide (**20**) was determined by X-ray crystallography and found to exist in the *1C* conformation.[20] The details of this X-ray analysis and those of other derivatives will form the subject matter of a future publication.

In summary, a new route to 4-amino-4,6-dideoxy sugars has been investigated and found to be successful. The fact that reduction of the oxime **6** affords almost exclusively the D-*talo* configuration may be ascribed to the steric accessibility of the lower side of the molecule as written; the approach of hydride to the upper side of the molecule is presumably hindered by both the C-6-methyl group and one of the methyl groups of the 2,3-*O*-isopropylidene bridge.

Experimental Section

All melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Thin layer chromatography was performed using silica gel H from Brinkman Instruments on 5 × 20 cm glass plates. Preparative thin layer chromatography was carried out on 20 × 40 cm glass plates coated with a 1-mm thickness of silica gel H. The following developing

(20) We are indebted to Dr. Milton Glick and coworkers of Wayne State University for the X-ray analysis.

solvents were used: (a) ethyl ether–*n*-pentane (1:1 v/v); (b) ethyl ether. Compounds were detected with a 6 *N* sulfuric acid spray followed by baking at 110° for 10–30 min. The bands on preparative plates were detected by spraying a 1-in. perpendicular band on both sides of the plates with sulfuric acid and baking. The bands were followed across the plates to the sprayed portions with ultraviolet light (Mineralight, U V S-11). pK_a data were determined in aqueous 50% methanol. Vpc analyses were performed on an F & M Scientific Corp. instrument (Model 810) fitted with a flame ionization detector. The following columns were used: (a) 10% Carbowax 20M on Chromosorb W, 2 ft × 0.25 in.; (b) 10% Carbowax 20M on Chromosorb W, 4 ft × 0.25 in. Nmr spectra were run in $CDCl_3$ using a Varian Associates A-60 spectrometer with tetramethylsilane as an internal standard. Pyridine was Merck Reagent Grade, dried over potassium hydroxide pellets. Microanalyses were performed by Midwest Microlab Inc., Indianapolis, Ind.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranosid-4-ulose (2).—Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**1**, 1.06 g) was dissolved in anhydrous dimethyl sulfoxide (4 ml) and dry pyridine (1 ml) and stirred under an atmosphere of dry nitrogen. Phosphorus pentoxide (1 g) was introduced quickly into the flask and the reaction mixture was heated at 60° for 1.5 hr. After it cooled to room temperature, dimethyl sulfoxide (2 ml), pyridine (0.5 ml), and phosphorus pentoxide (1 g) were added, and the heterogeneous mixture was heated at 60° for an additional 1.5 hr. This procedure was repeated (two to three times) until vpc analysis on column a (160°) showed little or no starting material. After the mixture cooled to room temperature, anhydrous K_2CO_3, equivalent to the P_2O_5 present, was added. Water was added dropwise until an evolution of gas occurred. Additional water was added cautiously until all gas evolution ceased. Then more water (10 ml) was added and the resulting homogeneous, dark reaction mixture was extracted with five 25-ml portions of *n*-pentane. The *n*-pentane extracts were dried (K_2CO_3) and concentrated *in vacuo* to give a crude oil. The oil was azeotroped several times with toluene to remove residual pyridine to yield compound **2**: 860 mg (81%); 96% pure by vpc analysis. A small portion was purified by preparative vpc on column a (130°). The physical constants are as follows: n^{24}D 1.4478; $[\alpha]^{27}$D +105° (c 0.71 in methanol). The literature[9,21] has reported $[\alpha]^{27}$D −107° (ethanol) for the corresponding L isomer.

Compound **2** was prepared also by oxidizing compound **1** with chromium trioxide–pyridine according to Collins and Overend[8,9] in 30% yield. This method required five successive oxidations to obtain compound **2** in 91% purity by vpc analysis.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (3).—Sodium borohydride (100 mg) was added in portions over a 10-min period to a vigorously stirred solution of the ketone **2** (394 mg, 95% purity) dissolved in dry methanol (3 ml) at 0°. Hydrogen evolved, and the solution warmed slightly. The reaction mixture was stirred an additional 50 min at room temperature. Analysis by thin layer chromatography in system a showed complete reaction. The methanol was removed *in vacuo* and water (2 ml) was added. The mixture was heated at 95° for 1 hr. The aqueous solution was cooled and extracted with five 10-ml portions of *n*-pentane. The *n*-pentane extracts were combined, dried (K_2CO_3), and concentrated *in vacuo* to afford compound **3** as a colorless oil, 337 mg (85%). Vpc analysis using column a (180°) showed three peaks with retention times of 5.8 (90%), 8.2 (2%), and 10.9 min (8%). These retention times correspond to compound **3** (*talo*), compound **1** (*manno*), and an unknown impurity, respectively. Compound **3** was characterized as the mesylate **4** and triacetate **5**.

Methyl 2,3,4-Tri-*O*-acetyl-6-deoxy-α-D-talopyranoside (5).—Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**3**, 67.5 mg) was dissolved in methanol (1 ml) containing 2 drops of concentrated hydrochloric acid. Analysis by thin layer chromatography in system a after 15 min showed no starting material and one spot at the origin. The solution was neutralized with silver carbonate, and the silver salts were removed by filtration through Hyflo Supercel. The filtrate was concentrated *in vacuo* to afford a gum which did not reduce Benedict's solution. The gum was dissolved in pyridine (0.5 ml) and acetic anhydride (0.5 ml), and was allowed to stand at room temperature for 2 days. The solvents were removed *in vacuo* with repeated azeotroping (toluene) to yield an oil which crystallized to give 41.7 mg (53%) of compound **5**, mp 91–93°. Recrystallization from chloroform–*n*-hexane afforded analytical **5**: mp 91–91.5°; $[\alpha]^{26}$D +76° (c 1.13 in methanol). The literature[8,9] has reported mp 91–92°, $[\alpha]^{20}$D −75.9° (c 3.9 in methanol), for the corresponding L isomer.

Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.63. Found: C, 51.49; H, 6.65.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-4-*O*-mesyl-α-D-talopyranoside (4).—Methyl 6-deoxy-2,3-*O*-isopropylidene-α,D-talopyranoside (**3**, 337 mg, 90% purity) was treated with mesyl chloride (0.23 ml) in pyridine (2 ml) at room temperature for 24 hr. The reaction mixture was poured onto an ice–water mixture (100 ml). The resulting precipitate was collected, washed well with water, and crystallized from aqueous ethanol to give compound **4**: yield, 330 mg (73%); mp 112–114° (needles). Three additional recrystallizations afforded needles with mp 116–117.5°, $[\alpha]^{27}$D +20.2° (c 0.8 in methanol).

Anal. Calcd for $C_{11}H_{20}O_7S$: C, 44.58; H, 6.79; S, 10.81. Found: C, 44.53; H, 6.61; S, 10.65.

Methyl 6-Deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranosid-4-ulose Oxime (6).—Methyl 6-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexopyranosid-4-ulose (**2**, 852 mg, 94% purity) was dissolved in pyridine–ethanol (1:1, 10 ml) containing hydroxylamine hydrochloride (900 mg). The mixture was heated under reflux for 2 hr, cooled, and evaporated *in vacuo*, and the residue was allowed to stand under 10 ml of water until it crystallized (10 hr). Recrystallization from *n*-hexane yielded compound **6**: mp 123–125°; 580 mg (64%). One more recrystallization from *n*-hexane afforded analytically pure material: mp 124.5–126°; $[\alpha]^{27}$D +155.3° (c 1.54 in CH_3OH); uv max (C_2H_5OH) 203 mμ (ε 6000); nmr, δ 1.48 (d, 3, J = 6 Hz, C-6-CH_3), 1.6 [d, 6, >C(CH_3)$_2$], 3.44 (s, 3, C-1-OCH_3), 4.38 (d, 1, J = 7.5 Hz, C-2-H), 4.63 (s, 1, C-1-H), and 4.78 (d, 1, J = 7.5 Hz, C-3-H) superimposed on 4.89 ppm (q, 1, J = 6 Hz, C-5-H).

Anal. Calcd for $C_{10}H_{17}NO_5$: C, 51.94; H, 7.41; N, 6.06. Found: C, 52.12; H, 7.40; N, 6.20.

Methyl 4-Amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (7).—A solution of oxime **6** (1.0 g) in dry tetrahydrofuran (2 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (0.5 g) in tetrahydrofuran (10 ml). After the addition was complete (1 hr), the reaction mixture was heated under reflux for an additional 20 hr. The reaction mixture was cooled to room temperature, and the excess hydride was decomposed with ethyl acetate followed by water, care being taken not to add a large excess of either reagent. The white precipitate was removed by filtration and washed with ethyl ether to yield compound **7** as a pale yellow oil, 895 mg (95%). Vpc analysis using column a (160°) showed one peak (trailing). The oil contained a small amount of the *manno* derivative **13** which was not detected at this stage. The oil was used without purification for subsequent reactions and characterized as the 2,4-dinitroanilino and the *N*-acetyl derivatives.

Methyl 4,6-Dideoxy-4-(2,4-dinitroanilino)-2,3-*O*-isopropylidene-α-D-talopyranoside (8).—Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**) was treated according to the method of Lloyd and Stacey[13] to give **8** in 67% yield following recrystallization from methanol with mp 138–140°. Recrystallization from chloroform–*n*-pentane and ethanol gave **8** having mp 139–140°, $[\alpha]^{27}$D −20° (c 1.23 in chloroform).

Methyl 4-Acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (9) and Methyl 4-Acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (14).—Impure methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**, 634 mg), containing a small amount of the *manno* isomer **13**, was treated with acetic anhydride (1 ml) and pyridine (3 ml) at room temperature for 0.5 hr. The solvents were removed *in vacuo* with azeotroping (toluene) to give a light brown oil which crystallized. Recrystallization from ethyl acetate afforded pure **9**: yield, 460 mg (61%); mp 149–150°; $[\alpha]^{27}$D +27.1° (c 0.51 in methanol).

Anal. Calcd for $C_{12}H_{21}NO_5$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.52; H, 8.34; N, 5.70.

An additional 40 mg (5%) of **9**, mp 148.5–150°, was obtained by repeated crystallizations from the mother liquor. The mother liquor was concentrated *in vacuo* to yield an oil (183 mg). The oil was applied to a preparative thin layer plate and developed in system b. Removal and processing of the band corresponding to the *talo* isomer **9** yielded another 40 mg (5%) of **9**, mp 148.5–

(21) P. M. Collins and W. G. Overend, *J. Chem. Soc.*, 3448 (1965).

150°, after recrystallization from ethyl acetate–*n*-hexane. The total yield of compound **9** was 71%.

Processing of the slower running band corresponding to the *manno* derivative **14** afforded 10.46 mg (1.3%), mp 86–92°, following crystallization from an ethyl ether–*n*-hexane mixture. An additional recrystallization afforded 4.0 mg of compound **14**, mp 96–98°, with prior softening at 92°. An infrared spectrum (chloroform) was very similar to that of compound **9**.

Methyl 4-Acetamido-4,6-dideoxy-α-D-mannopyranoside (15).—Methyl 4-acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-mannopyranoside (**14**, 3.03 mg) was dissolved in water (0.5 ml). The mixture was brought to pH 3.0 (pH paper) by the addition of two drops of 0.1 *N* hydrochloric acid. The reaction mixture was heated at 95° for 0.5 hr, cooled, and lyophilized to afford a white solid. The solid was crystallized from an ethanol–ethyl ether–*n*-hexane mixture to yield compound **15** as needles: yield, 1.76 mg (69%); mp 182–183°. A mixture melting point with authentic **15**,[22] mp 184–185°, was undepressed and the infrared spectra (KBr) of the two compounds were identical.

Methyl 4-Amino-4,6-dideoxy-α-D-talopyranoside Hydrochloride (16).—Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**, 249.5 mg) was dissolved in water (5 ml) at pH 3.0 (pH paper, hydrochloric acid) and heated at 95° for 2 hr. The solution was treated with charcoal and concentrated *in vacuo* at room temperature to yield a hygroscopic semisolid. Absolute ethanol was added followed by dry ethyl ether (dropwise to the turbidity point) to effect crystallization of compound **7**: 154.5 mg (63%); mp 169–170.5° dec. Two recrystallizations from an absolute ethanol–dry ethyl ether mixture yielded pure **16** as needles: mp 177–177.5° dec; $[\alpha]^{27}D$ +99.3° (*c* 0.66 in water); pK_a 8.45.

Anal. Calcd for $C_7H_{16}ClNO_4$: C, 39.35; H, 7.55; N, 6.56. Found: C, 39.36; H, 7.50; N, 6.75.

Methyl 4-Acetamido-4,6-dideoxy-α-D-talopyranoside (17).—Methyl 4-acetamido-4,6-dideoxy-2,3-*O*-isopropylidene-α-n-talopyranoside (**9**, 200 mg) was added to 3 ml of water at pH 3.0 (pH paper, hydrochloric acid) and heated at 95° for 1 hr. Lyophilization of the solution afforded **17** as a solid: 158 mg (94%); mp 166–168° dec, turning brown at 120°. Recrystallization from an ethanol–ethyl ether–*n*-pentane mixture yielded 100 mg (59%) of pure **17**: mp 182–183° dec, with some softening at 168°; $[\alpha]^{27}D$ + 167.5° (*c* 0.69 in methanol); $[\alpha]^{27}D$ +139.5° (*c* 0.38 in water). An infrared spectrum showed *N*-acetyl absorption at 5.95 μ and no *O*-acetyl absorption. A mass spectrum was essentially identical with the mass spectra of other 4-acetamido sugars except for minor variations in peak intensity. A mixture melting point with authentic *manno* derivative **15** was depressed.

Anal. Calcd for $C_9H_{17}NO_5$: C, 49.30; H, 7.82; N, 6.39. Found: C, 49.46; H, 7.96; N, 6.26.

Methyl 4-Acetamido-2,3-di-*O*-acetyl-4,6-dideoxy-α-D-talopyranoside (18). A.—Methyl 4-acetamido-4,6-dideoxy-α-D-talopyranoside (**17**, 65.5 mg) was dissolved in acetic anhydride (0.5 ml) and pyridine (0.5 ml) and allowed to stand at room temperature for 18 hr. Processing in the usual manner afforded pure **18** [79.3 mg (88%); mp 135–135.5°; $[\alpha]^{27}D$ +82° (*c* 0.49 in chloroform); $[\alpha]^{27}D$ + 67.8° (*c* 0.82 in methanol)] after one recrystallization from an ethyl ether–*n*-pentane mixture. The mass spectrum of **18** was essentially identical with the mass spectra of other triacetates of 4-amino sugars except for minor variations in peak intensity. The nmr of compound **18** showed δ 1.15 (d, 3, J = 6.8 Hz, C-6-CH_3), 1.96 [s, 3, axial[23] C-4-NHC(O)CH_3], 2.03 [s, 3, equitorial[23] C-3-OC(O)CH_3], 2.14 [s, 3, axial[23] C-2-OC(O)CH_3], 3.37 (s, 3, C-1-OCH_3), *ca.* 4.2 (m, 2, C-4-*H*, C-5-*H*), 4.62 (broad s, $J_{1,2}$ = 0–1 Hz, C-1-*H*), 5.1 (d, 1, $J_{1,2}$ = 0–1 Hz, $J_{2,3}$ = 4 Hz, C-2-*H*), 5.25 (t, 1, $J_{2,3}$ = 4 Hz, $J_{3,4}$ = 4 Hz, C-3-*H*), and 6.16 ppm (broad d, 1, C-4-N*H*).

Anal. Calcd for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62. Found: C, 51.76; H, 6.98; N, 4.88.

B.—Methyl 4-amino-4,6-dideoxy-α-D-talopyranoside hydrochloride (**16**, 15.16 mg) was converted into its free base using methanolic Dowex 1 (–OH). The free base was dissolved in pyridine (1 ml) and acetic anhydride (2 ml) and allowed to stand at room temperature for 14 hr. Processing in the usual manner yielded a gum which crystallized: yield, 17.7 mg (84%); mp 128–132°. Recrystallization from a chloroform–*n*-hexane mixture gave compound **18**: yield, 12.2 mg (57%); mp 134–136°. A mixture melting point determination with a sample of **18** prepared from *N*-acetyl derivative **17** was undepressed.

Methyl 4,6-Dideoxy-2,3-*O*-isopropylidene-4-(*N*-methylamino)-α-D-talopyranoside Hydrochloride (11).—Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**, 497 mg) was added to a mixture of chloroform (2 ml), water (4 ml), and sodium bicarbonate (300 mg) at 0°. Ethyl chlorocarbonate (0.5 ml) in chloroform (2 ml) was added dropwise with vigorous stirring over a period of 2 hr. The layers were separated and the aqueous layer was extracted with two additional 4-ml portions of chloroform. The extracts were combined, dried (K_2CO_3), and concentrated *in vacuo* to yield **10** as a heavy oil. Compound **10** was crystalline below room temperature. Without purification, the *N*-carboethoxy derivative (**10**) was treated with lithium aluminum hydride (430 mg) in 10 ml of ethyl ether under reflux for 12 hr. The reaction mixture was cooled and the excess hydride decomposed with ethyl acetate and water, care being exercised not to add an excess of either reagent. The inorganic salts were removed by filtration and washed well with ethyl ether. The combined washings and filtrate were concentrated *in vacuo* to afford an oil. The oil was rendered anhydrous by repeated evaporation with absolute ethanol and dissolved in absolute ethanol (2 ml) and dry ethyl ether (5 ml). Anhydrous hydrogen chloride in isopropyl alcohol was added dropwise with swirling to pH 3–4 (pH paper). Ethyl ether and *n*-pentane were added to incipient turbidity to effect crystallization of the amine hydrochloride **11** as dense crystals: yield, 400 mg; mp 174–175° dec; $[\alpha]^{28}D$ +86.2° (*c* 0.76 in methanol); pK_a 7.08. A second crop of 60 mg, mp 173–174.5° dec, was also obtained. The total yield was 76%.

Anal. Calcd for $C_{11}H_{22}ClNO_4$: C, 49.33; H, 8.28; N, 5.23. Found: C, 49.52; H, 8.50; N, 5.36.

Methyl 4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-2,3-*O*-isopropylidene-α-D-talopyranoside Hydrochloride (12).—Methyl 4-amino-4,6-dideoxy-2,3-*O*-isopropylidene-α-D-talopyranoside (**7**, 619.6 mg) was stirred under hydrogen, at atmospheric pressure in distilled *p*-dioxane (2 ml) containing aqueous 36% formaldehyde (0.52 ml) and 10% palladium on carbon (500 mg). After 4 days, vpc analysis using column a (150°) showed no starting material (retention time 10.5 min) and two peaks with retention times of 3.4 (4%) and 5.1 min (96%). The catalyst was removed by filtration using a Hyflo Supercel bed and washed well with absolute ethanol The washings and filtrate were combined and evaporated *in vacuo*. The resulting oil was azeotroped twice with absolute ethanol (3 ml), dissolved in absolute ethanol (1 ml) and dry ethyl ether (3 ml), and adjusted with dry hydrogen chloride in isopropyl alcohol to pH 4 (pH paper). Addition of ethyl ether to incipient turbidity effected crystallization of the *N*,*N*-dimethylamino derivative **12**: yield, 600 mg (75%); mp 196–198° dec. Recrystallization using an ethanol–ethyl ether mixture afforded 540 mg (68%), mp 202–203° dec. A small portion was recrystallized from an ethanol–ethyl ether and a methanol–ethyl ether mixture to give pure compound **12**: mp 205–206° dec; $[\alpha]^{28}D$ +90° (*c* 0.65 in methanol); pK_a 6.69.

Anal. Calcd for $C_{12}H_{24}ClNO_4$: C, 51.14; H, 8.58; N, 4.97. Found: C, 51.42; H, 8.52; N, 5.18.

Methyl 4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside Picrate (19).—Methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-2,3-*O*-isopropylidene-α-D-talopyranoside hydrochloride (**12**, 100.9 mg) was heated in water (2 ml) at pH 3.0 (pH paper, hydrochloric acid) at 95° for 20 hr. The reaction mixture was cooled and lyophilized to yield a yellow hard foam. The foam was dissolved in methanol. The solution was placed on a Dowex 1 (–OH) column and eluted with methanol. The eluent was concentrated *in vacuo* to yield the free base of compound **19** as a gum. The gum was dissolved in absolute ethanol and picric acid (82 mg) in ethanol was added. The solvent was removed *in vacuo* to yield a gum which crystallized when triturated under ethyl ether: yield, 145 mg (94%); mp 172–174°. Recrystallization from hot ethyl acetate afforded material with mp 173–174.5°; $[\alpha]^{27}D$ +62.8° (*c* 0.88 in methanol); pK_a 7.70. Further recrystallizations failed to raise the melting point.

Anal. Calcd for $C_{15}H_{22}N_4O_{11}$: C, 41.48; H, 5.11; N, 12.85. Found: C, 41.72; H, 5.30; N, 13.46.

Methyl 4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside Methiodide (20).—Methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-2,3-*O*-isopropylidene-α-D-talopyranoside hydrochloride (**12**, 44.84 mg) was hydrolyzed as described in the preparation of compound **19** to obtain the free base of compound **19**. The

(22) A sample was generously provided by Mr. S. K. Gupta of this laboratory.

(23) L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964).

free base was dissolved in methyl iodide (2 ml) and methanol (1 ml) and refluxed for 0.5 hr. Dilution of the reaction mixture with ethyl ether after cooling induced crystallization. The product was recrystallized from a methanol–ethyl ether mixture to yield compound **20** as needles: yield, 29.12 mg (65%); mp 234–236° dec. Three additional recrystallizations gave a pure product having constant mp 238–238.5° dec; $[\alpha]^{29}D$ +50.7° (c 0.523 in methanol).

Anal. Calcd for $C_{10}H_{22}INO_4$: C, 34.59; H, 6.40; N, 4.03. Found: C, 34.86; H, 6.69; N, 4.10.

Methyl 2,3-Di-*O*-acetyl-4,6-dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranoside (21).—Methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-2,3-*O*-isopropylidene-α-D-talopyranoside hydrochloride (**12**, 200 mg) was hydrolyzed as described in the preparation of compound **19** to obtain the free base of compound **19** as a gum, 121 mg (88%). The gum was dissolved in acetic anhydride (1 ml) and pyridine (1 ml) and allowed to stand at room temperature for 3 days. Removal of the solvents *in vacuo* with azeotroping (toluene) yielded 170 mg of crude solid. Recrystallization from hot *n*-hexane gave 110 mg (54% for two steps): mp 84–86°; $[\alpha]^{29}D$ +107° (*c* 6.60 in methanol); pK_a 5.78; nmr δ 1.44 (d, 3, $J_{5,6}$ = 7 Hz, C-6-CH_3), 2.0 [s, 3, equitorial[23] C-2-OC(O)CH_3], 2.13 [s, 3, axial[23] C-3-OC(O)CH_3], 2.2 [s, 6, -N(CH_3)$_2$], 2.44 (q, 1, $J_{3,4}$ = 3 Hz, $J_{4,5}$ = 5.5 Hz, C-4-*H*), 3.44 (s, 3, C-1-OCH_3), 4.35 (octet, 1, $J_{5,6}$ = 7 Hz, $J_{5,4}$ = 5.5 Hz, C-5-*H*), 4.73 (d, 1, $J_{1,2}$ = 0 Hz, $J_{2,3}$ = 1.2 Hz, C-2-*H*), 4.79 (s, 1, $J_{1,2}$ = 0 Hz, C-1-*H*), and 5.66 ppm (unresolved q, 1, C-3-*H*).

Anal. Calcd for $C_{13}H_{23}NO_6$: C, 53.97; H, 8.01; N, 4.84. Found: C, 54.15; H, 8.26; N, 4.73.

The hydrochloride salt of compound **21**, compound **22**, had mp 209–210° dec.

4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-β-D-talopyranose Hydrochloride (**23**), and 4,6-Dideoxy-4-(*N*,*N*-dimethylamino)-α-D-talopyranose Hydrochloride (**24**).—Methyl 4,6-dideoxy-4-(*N*,*N*-dimethylamino)-2,3-*O*-isopropylidene-α-D-talopyranoside (compound **12**, 257.1 mg) was heated at 95° in 1.0 *N* hydrochloric acid (3 ml) for 20 hr. The reaction mixture was treated with charcoal, cooled, and lyophilized to yield a foam. The foam was azeotroped twice with an ethanol–toluene mixture. Crystallization of the reaction mixture was accomplished by dissolving it in hot methanol (*ca.* 5 ml), cooling, and adding ethyl ether to incipient turbidity. As crystals deposited over a period of several days, more ethyl ether was added. The yield was 170 mg (96%) of a mixture of anomers **23** and **24**, as evidenced by a mp 140–175° dec. A predominance of the β anomer **23** was obtained by slow recrystallization from a dilute methanol–ethyl ether mixture seeded with the β anomer. After two recrystallizations the yield was 90 mg (51%): mp 154–156° (slight turbidity in melt, cleared at *ca.* 170°) (one more recrystallization lowered the melting point to 152–154°); $[\alpha]^{29}D$ *ca.* 7 → 21° (0.5 hr) (c 0.5 in water); pK_a 8.22.

Anal. Calcd for $C_8H_{18}ClNO_4$: C, 42.20; H, 7.97; N, 6.15. Found: C, 42.46; H, 7.98; N, 6.42.

The α anomer **24** was obtained by extracting the crude mixture of α and β anomers, mp 140–175° dec, with several small volumes of hot ethanol. The residue was compound **24**: mp 180–182° dec, with slight softening at 155°; $[\alpha]^{24}D$ 30.8 → 19.0° (0.75 hr) → 19.5° (22 hr); pK_a 7.60.

Anal. Calcd for $C_8H_{18}ClNO_4$: C, 42.20; H, 7.97; N, 6.15. Found: C, 41.97; H, 7.84; N, 6.07.

Registry No.—**2**, 15830-63-4; **4**, 15830-64-5; **5**, 15830-76-9; **6**, 15830-65-6; **7**, 15830-66-7; **8**, 15830-67-8; **9**, 15856-43-6; **11**, 15889-54-0; **12**, 15830-68-9; **14**, 15856-44-7; **15**, 15856-45-8; **16**, 15830-69-0; **17**, 15856-46-9; **18**, 15856-47-0; **19**, 15830-70-3; **20**, 15830-71-4; **21**, 15830-72-5; **22**, 15830-73-6; **23**, 15830-74-7; **24**, 15830-75-8.

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Nucleosides. L. Synthesis of 2,3′-Imino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine and Related Derivatives[1]

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Reaction of 5′-deoxy-5′-iodo-3′-*O*-mesylthymidine (**3**) with silver acetate in methanol afforded the 2,5′-anhydro derivative of 3′-*O*-mesylthymidine (**4**) in good yield which, by treatment with liquid ammonia, gave 2,3′-imino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (**6a**). Compound **6a** was also prepared from the 2-*O*-methyl derivative **8**. Reaction of the 2,5′-anhydro nucleoside **4** with methylamine, hydroxylamine, and hydrazine yielded the corresponding cyclic *N*-methyl, *N*-hydroxy, and *N*-amino derivatives **6b–d**. In the above reactions of **4** or **8** with amines the 2,3′-imino derivatives **6** formed *via* the isocytosine intermediate **5**. The reactions and ultraviolet, pK_a, and pmr data of the 2,3′-imino derivatives **6** are reported and discussed.

Arabinosylcytosine,[3] arabinosyl-5-fluorouracil,[4] and arabinosyl-5-fluorocytosine[5] have demonstrated interesting biochemical and chemotherapeutic activity.[6] In the synthesis of these biologically active compounds, 2,2′-anhydro-1-(β-D-arabinofuranosyl) uracil,[7] and 5-fluorouracil[4] and -cytosine[3,8] (**1a** and **b**, Figure 1) have been important intermediates. In order to obtain pyrimidine nucleosides of modified biological activity, the synthesis of the nitrogen isostere (**6**, Figure 2) of 2,3′-anhydro-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine[9] (**2**, Figure 1) was undertaken. The chemistry of **2** and its derivatives have been studied extensively in this and other laboratories.[9–11] Our recent chemical studies[8] on 2-aminopyrimidine nucleosides suggested that a 2,2′- or 2,3′-imino nucleoside may conceivably act as a chemical precursor for the synthesis of nucleosides containing an amino group in the "up" configuration in the sugar moiety.

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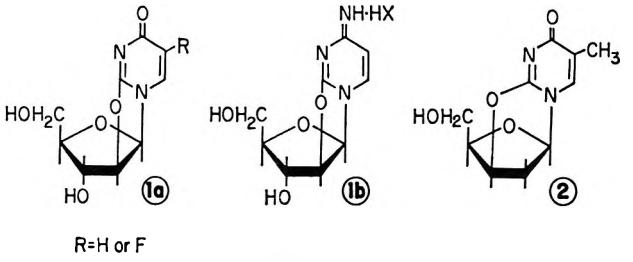


Figure 1.

We have shown[8] that treatment of the known[12] 2′,3′-*O*-isopropylidene-2,5′-anhydrouridine with liquid ammonia at room temperature for 18 hr converted it *directly* into 2′,3′-*O*-isopropylideneisocytidine. It was envisioned that, if a 2,5′-anhydro nucleoside contained a leaving group in the "down" configuration in the sugar moiety, reaction of such a compound with ammonia should lead first to an isocytidine derivative. This derivative should then undergo an intramolecular displacement reaction by the 2-amino group of the aglycon resulting in the formation of a nitrogen bridge analog of an anhydro nucleoside.

As a model compound, the 2,5′-anhydro derivative of 3′-*O*-mesylthymidine (**4**, Figure 2) was prepared in good yield by reaction of the 5′-iodo nucleoside (**3**)[9] with silver acetate in methanol. Proof that **4** is a 2,5′-anhydro nucleoside is shown by the dissimilarity of its melting point, optical rotation, ultraviolet spectral properties, and pmr data (Table I) from the known[9,10] 2,3′-anhydro isomer **7**.[13] Treatment of **4** with liquid ammonia for 5 days at room temperature yielded a crystalline product whose elemental analysis agreed with the 2,3′-imino structure (**6a**). Proof of structure **6a** rests on the following data. The ultraviolet absorption spectral patterns of **6a** under neutral and acidic conditions resemble that of 1-β-D-arabinofuranosyl-5-methylisocytosine (**9**) (Table II). The pmr spectrum of **6a** in DMSO-d_6 (Table I) shows a broad singlet (1 H) at δ 9.62 (>NH) and a broad triplet (1 H) at 5.14 (-OH); both were exchanged by the addition of D_2O. As expected the H_3' signal in **6a** is considerably upfield when compared with the H_3' signal of 2,3′-anhydro-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (**2**) (Table I).

The methylimino derivative **6b** was prepared in almost quantitative yield by reaction of **4** with methylamine for 5 days at room temperature. The ultraviolet absorption characteristics of **6b** were similar to those for **6a** under acid or neutral conditions. No dissociation of **6b** was observed spectrally in strong alkali. In contrast, the imino derivative **6a**, which has one dissociable proton associated with the pyrimidine, dissociates in strong alkali. As discussed below the pmr data also supports the methylimino bridge in **6b**.

Treatment of the 2,5′-anhydro nucleoside (**4**) with methanolic hydroxylamine or with anhydrous hydrazine gave the *N*-hydroxy and *N*-amino derivatives (**6c** and **6d**, R = OH and NH_2, respectively) in high yields. It is clear that, in the conversion of **4** → **6** by amines, the isocytidine derivatives (**5**) were intermediates.

An alternate route to the synthesis of **6a** was achieved. The 2-methoxy derivative **8** was prepared by treatment of anhydro nucleoside **4** with hot methanol containing triethylamine. Reaction of **8** in liquid ammonia for several days afforded **6a** in high yield.

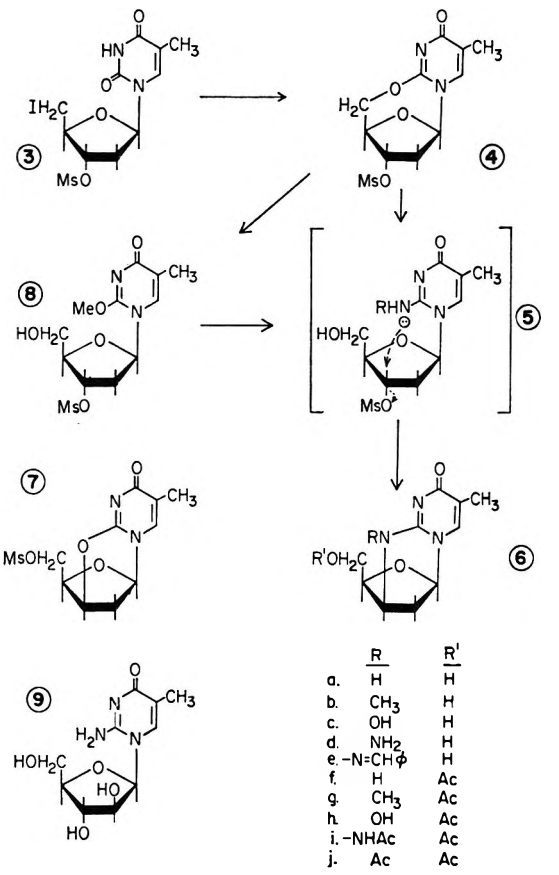


Figure 2.

Treatment of the hydrazino derivative (**6d**) with nitrous acid converted it into **6a**. Reaction of **6d** with benzaldehyde in ethanol containing hydrochloric acid produced the benzalamino derivative **6e** (R = C_6H_5-CH=N—).

Treatment of **6a** with excess acetic anhydride in pyridine at 60–70° for several hours gave an unstable diacetyl derivative **6j** (not isolated)[14] which hydrolyzed slowly to the 5′-*O*-acetate (**6f**). In similar manner, the hydroxylamino derivative **6c** also gave an unstable diacetate which was converted into **6h**. The methyl analog **6b** formed the monoacetate **6g** directly, whereas the hydrazino derivative **6d** gave a stable diacetate **6i**. All the isolated acetate derivatives (**6f–i**) were extremely soluble in water.

A comparison of the acetylation reactions of **6a–d** with the "uncyclized" 1-β-D-arabinofuranosylisocytosine (**10**)[15] (Figure 3) is of interest. Acetylation of **10** afforded a stable crystalline tetraacetate (**11**) which was hydrolyzed in dilute acid (3 hr) at room temperature to the known triacetate (**12**)[16] of 1-β-D-arabinofuranosyluracil. This behavior of **11** is to be contrasted with that of the diacetate of **6a** which, when treated with acid, yields the monoacetate **6f** without cleavage of the

(12) D. M. Brown, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 868 (1957).

(13) It should be noted that the conversion of **3** → **4** offers independent confirmation of the structure of **3**. Compound **3** had been prepared[9] by heating 3′,5′-di-*O*-mesylthymidine with sodium iodide in dry acetone.

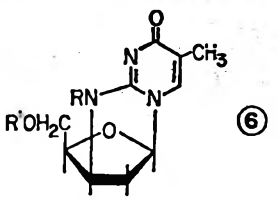
(14) The actual position of the *N*-acetyl group in structure **6j** (Figure 2) is not known. For convenience the acetyl group is drawn on the bridge nitrogen.

(15) D. M. Brown, D. B. Parihar, A. R. Todd, and S. Varadarajan, *ibid.*, 3028 (1958).

(16) D. M. Brown, A. R. Todd, and S. Varadarajan, *ibid.*, 2388 (1956).

TABLE I

PROTON MAGNETIC RESONANCE DATA



⑥

Compd No.	R	R′	H_6	C_5–CH_3	H_1'	$H_2'(H_2')$	H_3'	H_4'	$H_5'(H_5')$	Acetyl	Miscellaneous	Solvent
	H	H	7.43	1.74	5.70	2.34	←~4.13→		3.60	...	(C_5')OH 5.14; >N—H 9.62	DMSO-d_6
6a	H	H	7.55	2.06	5.98	2.73	←~4.66→		4.25	...	...	TFA
	H	H	7.52	1.89	5.88	2.54	←~4.41→		3.90 ($J_{4',5'} \sim 6.0$)	...	...	D_2O
6b	CH_3	H	7.60	2.10	5.98	2.78	←~4.70→		4.25 ($J_{4',5'} \sim 5.0$)	...	>N—CH_3 3.57	TFA
6c	OH	H	7.57	2.09	5.94	2.92	←~4.75→		4.35 ($J_{4',5'} \sim 4.0$)	...	...	TFA
6d	NH_2	H	7.52	1.77	5.77	2.39	←~4.27→		~3.67	...	(C_5')OH 4.92; >N—NH_2 5.01	DMSO-d_6
6f	H	Ac	7.35	1.93	5.81	2.52	←~4.48→			2.08	>N—H 10.48	$CDCl_3$
6g	CH_3	Ac	7.56	1.97	5.95	2.58	←~4.39→			2.09	>N—CH_3 3.33	$CDCl_3$
6h	OH	Ac	7.37	1.95	5.80	2.72	4.89	←~4.54→		2.08	>N—OH 11.98	$CDCl_3$
6i	NHAc	Ac	7.38	1.95	5.76	~2.49 (~2.99)	←~4.47→			2.06	>N—Ac 2.12; >N—H 11.70	$CDCl_3$
1-(2′-Deoxy-2,3′-anhydro-β-D-*threo*-pentofuranosyl)-thymine (2)			7.70	1.80	5.96	~2.56	5.37	4.32	3.59	...	(C_5')OH 5.10	DMSO-d_6
1-(2′-Deoxy-2,5′-anhydro-3′-*O*-methanesulfonyl-β-D-*threo*-pentofuranosyl)thymine (4)			7.78	1.83	6.16	2.72	5.55	4.81	4.68 (4.14)	...	—O—Mes 3.34	DMSO-d_6
1-(2′-Deoxy-2,3′-anhydro-5′-*O*-methanesulfonyl-β-D-*threo*-pentofuranosyl)thymine (7)			7.66	1.79	5.97	2.60	5.41	←~4.44→		...	—O—Mes 3.23	DMSO-d_6
1-β-D-Arabinofuranosylisocytosine (10)			7.57	H_5 = 5.50	5.82	4.18	←~3.80→			...	>N—H 6.78; —OH (three protons), broad peak 4.89–5.98	DMSO-d_6
1-β-D-Arabinofuranosylisocytosine tetraacetate (11)			7.94	H_5 = 6.03	6.61	5.58	5.23	←~4.41→		2.00; 2.13 (nine protons)	>N—H 12.83	DMSO-d_6

TABLE II

SPECTROPHOTOMETRIC[a] AND pK_a[b] DATA

	pH[c]	λ_{max}, mμ	ε	λ_{min}, mμ	ε	pK_a
2,3′-Methylimino- (**6b**)	0	244, 270	9,450, 8,030	220, 260	6,150, 7,760	2.64
	6.9	228, 268–270sh	20,500, 3,360			
2,3′-Imino- (**6a**)	0	240, 266	7,440, 8,100	218, 250	4,850, 7,050	3.33
	7.7 and 12	213, 257–269sh	22,700, 4,000			
	13	267–269sh	3,810			
	7 *N* KOH[d]	237	19,800			
2,3′-Hydroxyimino- (**6c**)	0	235, 264–265sh	8,980, 8,640	225	4,460	3.26[e]
	6.8	228, *265*	20,240, 5,390			
	14	241, 269	17,200, 11,090	269	10,970	
2,3′-Ammoimino- (**6d**)	0	245, 267	8,760, 8,290	221, 257.5	5,560, 8,106	3.60
	6.9	227, *267*	20,340, 4,160			
Arabinofuranosyl-5-methyl-isocytosine (**9**)[f]	0	225, 260	9,130, 8,300	240	6,430	3.80 ± 0.1
	Water	204, 260, *214*, *228*	20,600, 6,740	246	5,910	
	13	262, *225*	7,050	247	5,900	
	5.6 *N* KOH	272–276	4,020	264	3,910	

[a] Italicized numbers refer to inflections; the term sh after the wavelength value refers to a shoulder. [b] The apparent pK_a values in this table are for basic dissociations and were determined spectrophotometrically with an accuracy of ±0.05 pH units unless otherwise indicated. The acidic dissociation observed in the high alkaline region in compounds **6a** and **9** were not determined. [c] The spectrum of the above compounds at pH 0 and 7 are those of pure cationic and neutral species, respectively. The spectrum of **6c** at pH 14 is that of pure anionic species. The spectrum of **6a** in 7 *N* KOH is mainly that of the anionic species. The spectrum of arabinosyl-5-methylisocytosine (**9**) in 5.6 *N* KOH is that of a mixture of neutral and anionic species. On the addition of concentrated hydrochloric acid to the 7 *N* and 5.6 *N* KOH solutions of **6a** and **9**, respectively, the acid spectra of these compounds were reconstituted. [d] The ε value for **6a** in 7 *N* NaOH is 1300 at 290 mμ (no maximum). Compare with the values for **9** (footnote *f*). [e] A second pK_a = 9.34 was also determined. [f] In 7 *N* KOH **9** showed maxima at 291 and 231 mμ (ratio 231:291 mμ of 16.0), minimum at 267 mμ as previously reported.[8]

2,3′-imino bridge.[17] Also, compound **6j** is converted into **6a** in alkali without cleavage of the nitrogen bridge. Treatment of **11** with aqueous 1 *N* alkali at room temperature overnight gave arabinosyluracil (**13**) directly. The conversion of **10** into **13** in 1 *N* alkali had been noted previously.[8] As suggested by the pmr spectrum of the tetraacetate of **11** in $CDCl_3$ (see discussion below), structure **11** (Figure 3) is represented in the acetimido rather than in the acetamido tautomeric form.

A preliminary comparison of the properties of the 2,3′-imino-bridged nucleosides (**6a** and **6b**) with the "oxygen isostere" **2** is also of interest. All of the 2,3′-imino nucleosides were stable under acid and basic conditions which would readily cause the 2,3′-anhydro nucleoside (**2**) to react. For instance, **6a** and **6b** were stable in strong aqueous alkali (7 *N* KOH) for 3 weeks at room temperature. By contrast, anhydro nucleoside **2** is easily cleaved in 0.1 *N* sodium hydroxide (24 hr) to 1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine.[9] These data shows that an "up" 3′-amino-3′-deoxy nucleoside cannot be obtained from the 2,3′-imino nucleosides **6a–d** under alkaline conditions. When the imino-bridged nucleoside (**6a**) was refluxed in 1 *N* hydrochloric acid for 1 hr, only a small amount of degradation occurred, though, after 2 days at reflux temperature, glycosyl cleavage was extensive. This slow degradation of **6a** is to be contrasted with the relatively rapid glycosyl cleavage of **2**, which occurs within 1 hr under similar reaction conditions.[9] When either **6a** or **2** was heated at 65° with liquid ammonia for 4 days, no reaction occurred and starting material was recovered.

The ionization constants and spectral data for the 2,3′-imino derivatives **6a–d** along with the related uncyclized derivative **9** are given in Table II. The ultraviolet spectra of the neutral and cationic species of compounds **6a–d** compared with those of derivative **9** show similarities suggesting the existence of similarly conjugated systems in all of these compounds. As expected, the neutral and cationic spectra of the imino compounds **6a–d** resemble each other more closely than they do the spectra of **9**. The similarity of the neutral and cationic spectra in the imino-bridged compounds **6a–d** suggest that all of these exist predominantly in the *p*-quinonoid form (2-amino-4-oxo) as the neutral species. One may conclude, further, that protonation of compounds **6a–d** occurs on the same site, probably on N_3.

As expected, the monoacetate derivatives of **6f–h** possessed ultraviolet spectral patterns similar with that of the unacetylated compounds (**6a–c**). On the other hand, the diacetate **6i** of the hydrazino derivative exhibited different spectra in water, acid, and base when it was compared with the unacetylated hydrazino derivative **6d**.

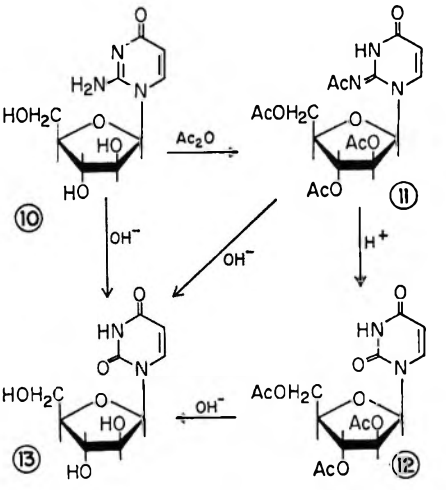


Figure 3.

(17) The behavior of acetate **11** in acid is to be further contrasted to the behavior of unacetylated **10**. Compound **10** (depending on concentration and type of acid) may give either 2,2′-anhydroarabinosyluracil or isocytosine as previously reported.[8]

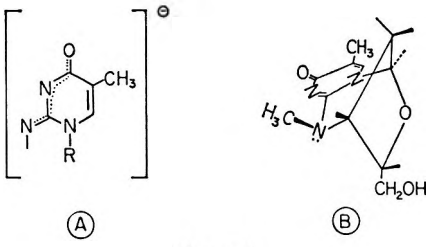


Figure 4.

When compared with the uncyclized 2-amino nucleoside **9**, the introduction of a 2,3′-imino bridge into a nucleoside (**6a–d**) produced an acid-strengthening effect (Table II). As might be expected, the smallest acid-strengthening effect (−0.2 pK units) was exhibited by the amino derivative **6d**. The "unsubstituted" imino derivative **6a** and the hydroxy derivative **6c** showed practically the same drop in pK_a (~0.4 pK units) compared with compound **9** (pK_a = 3.80). As seen in Table II the weakest base in the series is the N-methyl derivative **6b** (pK_a = 2.64) which exhibits a lower pK_a than its unmethylated analog **6a** (pK_a = 3.33). The lower basicity of the N-methyl derivative **6b** *vs.* **6a** may be attributed to a decrease of hydrogen bonding to water in the cation **6b** compared with that in the cation **6a**.

Mention should be made of the second pK_a observed spectrally under alkaline conditions in the 5-methylisocytosine nucleosides **6a**, **6c**, and **9**.[18] The second dissociation in these compounds is attributable to proton removal from the aglycon of the neutral species. The N-hydroxy derivative **6c** has a second pK_a at 9.34. The second pK_a (not determined) of compounds **6a** and **9** is found in the high alkaline range as evidenced by the striking ultraviolet spectral changes observed in alkali. As seen in Table II the ultraviolet spectrum of the 2,3′-imino derivative **6a** and that of the uncyclized 5-methylisocytosine nucleoside **9** in 0.1 N sodium hydroxide (pH 13) are very different from the spectra observed for these compounds in 7 N and 5.6 N potassium hydroxide, respectively. The similarity of the spectral changes in aqueous alkali exhibited by the 2,3′-imino nucleoside **6a** and the 5-methylisocytosine nucleoside **9** strongly suggest a common anion. A representation of this anion is shown in Figure 4A. It is noteworthy that the spectral curve of 1-methylcytosine (a 4-amino derivative) in 6 N sodium hydroxide is identical with that found for pH 7–14.[19] As expected, the spectrum of the N-methyl derivative **6b** (which has no dissociable proton on the aglycon) is the same in 0.1 N sodium hydroxide as in 7 N potassium hydroxide. Like **6b** the aglycon of the N-amino derivative **6d** did not exhibit a dissociation in the ultraviolet in strong alkali.

Proton Magnetic Resonance Data.—The pmr data for the nitrogen bridge analogs of anhydro nucleosides are listed in Table I and are consistent with the structures assigned. Compounds **6b** and **6c** were soluble with difficulty in all solvents but trifluoroacetic acid (TFA). The 5′-O-acetates (**6f–i**) were more soluble and their pmr spectra were determined in $CDCl_3$ solution. The nitrogen-bridged compounds gave poorly resolved spectra in all cases. The only signal which could be resolved was that of the C_5-methyl occurring at δ 1.74–2.09 which showed, in most cases, the characteristic J_{CH_3,H_6} ~1.0 Hz. The other signals were either broad singlets (half-band widths of 4.2–6.0 Hz) or broad multiplets. All peaks assigned to –NH or –OH were shown to disappear upon addition of D_2O to the solution.

The N-methyl compound **6b**, although sparingly soluble in DMSO-d_6, did at least show a sharp singlet at δ 3.14 characteristic of an N–CH_3 resonance. That the N-methyl peak in the spectrum of **6b**, and also of **6g**, was unsplit is added proof of the cyclic nature of the compounds **6**.

The pmr data for the nitrogen bridge compounds can be compared with those of 2,3′-anhydro compounds **2** and **7** and 2,5′-anhydro compound **4** (Table I). The C_5' protons of **4** form a quartet, an AB subspectrum, δ 4.14 and 4.68 ($J_{4',5'}$ ~ 1.0 Hz, $J_{5',5'}$ ~ 12.5 Hz) which is characteristic of 2,5′-anhydro nucleosides.[20] On the other hand, the 2,3′-anhydro compounds and the nitrogen-bridged compounds (**6**) show the C_5' protons, when discernable, as a doublet (pseudo-doublet), which is characteristic of 2,3′- and 2,2′-anhydro nucleosides.[20]

The H_3' chemical shifts for the N-bridged compounds (δ ~4.13–4.75 for the average of the H_3' and H_4' chemical shifts) are found to higher field than the H_3' chemical shifts for the anhydro compounds (δ 5.37–5.55) in accordance with the greater electronegativity of oxygen *vs.* nitrogen.

Compounds **6** may be viewed as derivatives of 2,4-diaza-6-oxabicyclo[3.2.1]octane (Figure 4B). In an attempt to determine the configuration of the N substituent in the bicyclo system pmr studies on compound **6g** were carried out in $CDCl_3$ at various temperatures. An extra peak at δ 11.72 was observed which integrated for ~0.6 protons and which disappeared upon addition of D_2O. No other extraneous peaks were found, however, and microanalytical and chromatographic data indicate that the impurity must be present in very small amount. The N-methyl peak at δ 3.33 remained a singlet at temperatures from 43 to −60°. Since the N-methyl peak did not split at lowered temperature, it indicates that the compound exists as a rapidly interconverting mixture of *exo* and *endo* N-methyl conformers owing to rapid nitrogen inversion in the bicyclic system. Very low energy barriers to nitrogen inversion have been found for saturated six-membered heterocycles.[21] A high percentage of conformers should exist at equilibrium with their methyl substituent in the *exo* orientation. The alternate conformer with an *endo* methyl group is disfavored owing to steric hindrance imposed by interaction with the bulky 4′-hydroxymethyl group of the sugar moiety (see Figure 4B).

An indication that the N-methyl substituent occupies predominantly the *exo* orientation is seen in the pmr data for **6i**. In all other compounds (**6**) in the series the bridge methylene protons (H_2') have nearly identical chemical shifts. With **6i** the two C_2' protons occur at δ 2.49 and 2.99. The proton at δ 2.49 is probably due to the H_2' on the same side as the bulky >N–NHAc moiety and its high-field shift may be due to the aniso-

(18) Appreciable changes in the ultraviolet spectrum of 2,3′-O-isopropylideneisocytidine, 1-β-D-arabinofuranosylisocytosine, and the 5-methylisocytosine derivative **9** under various alkaline conditions were reported and dissociation of the isocytosine moiety was suggested.[8] The present study confirms this hypothesis.

(19) T. Ueda and J. J. Fox, *J. Amer. Chem. Soc.*, **85**, 4024 (1963).

(20) R. J. Cushley, unpublished results.

(21) A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.*, **80**, 5203 (1958).

tropic effect of the acetyl group. Diamagnetic effects due to neighboring acetyl groups have been reported recently.[22] The nonequivalence of the two $H_{2'}$ signals is not found in the other cases since the anisotropy is known to decrease rapidly with distance.[23]

The pmr data for 1-β-D-arabinofuranosylsocytosine (**10**) and its tetraacetate (**11**) are also given in Table I. Since the C_5-methyl group is no longer present, column 3 contains the chemical shift of H_5. An interesting effect is seen in the spectrum of **11** in dry DMSO-d_6. The H_5 signal at δ 6.03 has a half-band width of 3.2 Hz while the H_6 signal has a half-band width of 2.0 Hz. Thus there is a long-range coupling of H_5 to H_3 of about 0.2–0.4 Hz which vanishes when D_2O is added to the solution. Cushley, *et al.*, have reported a long-range coupling between H_5 and H_3 (J = 1–2 Hz) for pyrimidine nucleosides and 1-methyluracil when dry DMSO-d_6 is used as solvent.[24] That such a long-range coupling is observed in the spectrum of compound **11**, and the magnitude is smaller than observed previously,[24] shows that at least part of the compound exists in the imino form as depicted in Figure 3.

Experimental Section

General Procedure.—Pmr spectra were determined with a Varian A-60 spectrometer fitted with a V-6057 variable-temperature accessory. Chemical shifts (δ) are given in parts per million (ppm) from internal TMS (DSS for the D_2O solutions). Ultraviolet absorption data were determined with a Cary recording spectrophotometer, Model 15. The apparent pK_a values were determined spectrophotometrically using buffers and techniques previously employed.[25] Infrared data were obtained using a Perkin-Elmer Model 221 spectrophotometer. Paper chromatograms were determined on Schleicher and Schuell paper No. 597 (ascending technique) using system A, acetone–chloroform–water (5:1:1), or system B, butanol–water–ethanol (40:19:11). Melting points of all compounds except **6b** were taken on a Thomas–Hoover capillary melting point apparatus. The melting point of **6b** was taken on a Mel-Temp apparatus. All melting points are corrected. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Pmr and ultraviolet absorption data are reported in Tables I and II, respectively.

2,5'-Anhydro-1-(2-deoxy-3-*O*-mesyl-β-D-*erythro*-pentofuranosyl)thymine (4).—The 5'-iodo nucleoside **3**[9] (25 g, 0.058 mol) was dissolved in 3 l. of methanol. Silver acetate (75 g) was added and the reaction mixture refluxed with stirring for 30 min. The hot reaction mixture was filtered using a filter aid of diatomaceous earth. Hydrogen sulfide gas was passed through the solution until all silver ions were removed. Norit was added to the silver sulfide suspension and the mixture was filtered using a Filter-aid pad. The colorless filtrate was aerated with nitrogen in order to drive off excess hydrogen sulfide. Precipitation of the anhydro nucleoside occurred. Filtration afforded 4.5 g, mp 180–183° dec.

Triethylamine (0.058 mol) was added to the filtrate which was then concentrated. An additional 7.3 g, mp 180–183° dec (total yield 67%), of **4** was obtained. A sample of **4** was recrystallized from 95% methanol. White, hair-like crystals appeared, mp 182–183° dec, $[\alpha]^{26}D$ +52° (*c* 0.4, DMF). The ultraviolet absorption properties in water were bands appearing at λ_{max} 248 mμ and λ_{min} 218 mμ.

Anal. Calcd for $C_{11}H_{14}N_2O_6S$: C, 43.70; H, 4.65; N, 9.27; S, 10.62. Found: C, 43.76; H, 4.70; N, 9.16; S, 10.70.

2-*O*-Methyl-3'-*O*-mesylthymidine (8).—To a suspension of 2,5'-anhydro nucleoside **4** (4 g, 0.013 mol) in methanol (1400 ml) was added triethylamine (80 ml). The mixture was refluxed for 3 hr during which time solution occurred. The reaction mixture was concentrated *in vacuo* to an amorphous white powder. The powder was crystallized from ethanol (~150 ml) to give white needles (3.9 g), mp 130–135°. A sample, on recrystallization, melted at 135–138°, $[\alpha]^{24}D$ +19° (c 0.6, DMF). The ultraviolet absorption properties in water were bands appearing at λ_{max} 254–255 and 227 mμ and λ_{min} 217 and 233 mμ. It was noted that the spectrum of **8** bears a striking resemblance to that of 2,2'-anhydro-1-β-D-arabinofuranosylthymine.[26]

Pmr spectrum in pyridine-d_5 consisted of H_6 (δ 8.10, doublet, J_{CH_3,H_6} = 1.1 Hz), OH(C-5') (δ 7.13, broad peak), $H_{1'}$ (δ 6.48, triplet, $J_{1',2'}$ = 7 Hz), $H_{3'}$ (δ 5.40, mulitplet), $H_{4'}$ (δ 4.65, multiplet), $H_{5'},H_{5'}$ (δ 4.19, broad singlet), $-OCH_3$ (δ 3.19, singlet), $-OSO_2CH_3$ (δ 3.45, singlet), $H_{2'},H_{2'}$ (δ 2.82, quartet, $J_{2',3'}$ = 4 Hz), C-CH_3 (δ 1.93, doublet). Upon addition of D_2O the peak at δ 7.13 disappeared and the peak at 4.19 became a pseudodoublet, $J_{4',5'}$ = 3.1 Hz).

Anal. Calcd for $C_{12}H_{18}N_2O_7S$: C, 43.11; H, 5.43; N, 8.38; S, 9.59. Found: C, 43.08; H, 5.63; N, 8.26; S, 9.66.

2,3'-Imino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6a). Method A.—The 2,5'-anhydro nucleoside **4** (0.8 g, 2.6 mmol) was allowed to react with liquid ammonia (40 ml) for 5 days at room temperature in a glass-lined steel bomb. Evaporation of the ammoniacal solution gave a white powder which was shown to contain only **6a** by chromatographic analysis. The product was dissolved in water and purified by absorption on a column of Dowex 50 (H^+, 100–200 mesh). The column was washed with water until the effluent was acid free, then eluted with 2 *N* NH_4OH. The ammonia eluates containing ultraviolet absorbing material were evaporated to a crystalline residue which was recrystallized from 90% ethanol. Compound **6a** crystallized as white prisms (0.5 g, 84%), mp 245° (sintering) and 265° dec (with effervescence), $[\alpha]^{25}D$ +23° (*c* 0.7, 0.1 *N* HCl).

Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.82. Found: C, 53.54; H, 5.87; N, 19.05.

Method B.—The 2-*O*-methyl nucleoside (**8**) (0.6 g, 1.8 mmol) was treated with liquid ammonia (40 ml) for 4 days at room temperature. Compound **6a** was isolated as described in method A. White prisms (0.29 g, 72%) were obtained, mp 250° (sintering) and 268° dec (with effervescence). The ultraviolet absorption spectra in acid and water, ir spectrum, and chromatographic properties of the product were identical with those of the compound obtained by method A.

2,3'-Methylimino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6b).—The 2,5'-anhydro nucleoside **4** (1.2 g, 4 mmol) was allowed to react with liquid monomethylamine (40 ml) for 5 days at room temperature. The monomethylamine was evaporated and a crystalline residue was obtained which by chromatographic analysis (systems A and B) showed only one blue fluorescent spot. Upon addition of water (20 ml) to the residue crystallization occurred: 0.9 g (98%) of **6b**, mp 265° (sintering) and 295° dec (with effervescence). The product on recrystallization from water (80 ml) afforded white needles (0.6 g), mp 334° (sintering) and 345° dec (with effervescence), $[\alpha]^{26}D$ ~0° (*c* 0.7, 0.1 *N* HCl). On evaporation the mother liquor yielded an additional 0.16 g, mp 270° (sintering) and 278° dec (with effervescence). The ir spectra of the low and high melting recrystallized products were identical as were their chromatographic properties.

Anal. Calcd for $C_{11}H_{15}N_3O_3$: C, 55.68; H, 6.37; N, 17.71. Found: C, 55.60; H, 6.32; N, 17.82.

2,2'-Hydroxyimino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6c).—A methanolic hydroxylamine solution was prepared by dissolving hydroxylamine hydrochloride (2.2 g, 32 mmol) in methanol (50 ml) containing phenolphthalein as indicator. Enough methanolic 1 *N* KOH (~40 ml) was added to the solution to produce a red color. To the precipitated KCl suspension a solution of hydroxylamine hydrochloride was added until a pH of about 7.4 was reached. The potassium chloride was removed by filtration.

The above filtrate was immediately added to a suspension of the 2,5'-anhydro nucleoside **4** (2 g, 6.6 mmol) in methanol (75 ml). Solution of **4** occurred upon reflux. After 2.5 hr of reflux, prisms of **6c** (1.1 g, 69%) crystallized from the hot solution and were removed by filtration. During the melting point determination, the compound darkened at 200° and decomposed with effervescence at 240°. Paper chromatography (system A)

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showed that the mother liquor contained **6c** (R_f 0.36) in addition to some starting material (**4**, R_f 0.90). Concentration of the mother liquor afforded additional **6c** (0.4 g), mp 190° (sintering) and 240° dec (with effervescence). Recrystallization of **6c** from water yielded prisms, mp 262° (sintering) and 274° dec (with effervescence), $[\alpha]^{25}D$ −17° (*c* 0.7, 0.1 *N* HCl).

6c gave an intense dark blue color with ferric chloride solution. Aqueous solutions of **6c** were slightly blue in color.

Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.20; H, 5.48; N, 17.57. Found: C, 50.28; N, 5.42; N, 17.70.

2,3′-Aminimino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6d).—The 2,5′-anhydro nucleoside **4** (2 g, 6.6 mmol) was allowed to react with anhydrous hydrazine (~15 ml) for 1 hr at room temperature. During this time solution of **4** occurred. The reaction mixture was taken to dryness *in vacuo* and dissolved in water. This mixture was evaporated *in vacuo* to dryness. The residue, which by chromatographic analysis (systems A and B) contained only one ultraviolet absorbing spot (**6d**), was dissolved in water and the solution neutralized with 2 *N* acetic acid. The product was purified by a batchwise treatment with Dowex 50 (H^+, 100–200 mesh). The resin was washed free of acid and treated with 2 *N* NH_4OH. The resin was removed by filtration and the ammonium hydroxide filtrate (~200 ml) was evaporated to dryness. On trituration with ethanol a white solid (1.3 g, 77%) was obtained, mp 230° (sintering) and 260° dec (with effervescence). Crystallization from methanol (80 ml) afforded rodlike crystals (0.8 g), mp 273–275° dec (with effervescence), $[\alpha]^{25}D$ +7° (*c* 0.8, 0.1 *N* HCl). On further concentration of the mother liquor an additional 0.26 g, mp 273–276° dec, was obtained.

Anal. Calcd for $C_{10}H_{14}O_3N_4$: C, 50.41; H, 5.92; N, 23.52. Found: C, 50.46; H, 5.89; N, 23.36.

2,3′-Imino-1-(5-*O*-acetyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6f).—To the 2,3′-imino compound **6a** (0.2 g, 0.9 mmol) suspended in pyridine (15 ml) was added acetic anhydride (5.3 mmol). The reaction mixture was allowed to stand overnight at room temperature. Ethanol was then added to the solution and the pyridine was removed *in vacuo* by repeated distillation with water and then ethanol. A glass (containing residual acetic acid) was obtained. Paper chromatography (system A) showed the presence of two ultraviolet absorbing products: the diacetate **6j** (R_f 0.92)[27] and the 5′-*O*-acetate **6f** (R_f 0.73). The glass was dissolved in ethyl acetate and 170 mg of white crystals of **6f** (mp 240° dec with prior shrinking) slowly (~1 day) appeared. (The diacetate **6j** remained in the mother liquor and was slowly converted into the monoacetate **6f**.) Recrystallization of **6f** from ethyl acetate gave rodlike crystals (90 mg), mp 260–265°, $[\alpha]^{25}D$ +35° (*c* 0.4, water). This product exhibited essentially the same ultraviolet spectral data in water, acid, and base as **6a** (Table II). Paper chromatography of **6f** in systems A and B showed one ultraviolet absorbing spot with R_f 0.80 and 0.64, respectively (nucleoside **6a**, R_f 0.54 and 0.47).

Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.38; H, 5.66; N, 15.96.

2,3′-Methylimino-1-(5-*O*-acetyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6g).—To 2,3′-methylimino **6b** (0.15 g, 0.63 mmol) suspended in pyridine (35 ml) was added acetic anhydride (1.6 mmol). The mixture was heated at 75° for 5 hr during which time solution of **6b** slowly occurred. The reaction mixture was allowed to stand overnight at room temperature. The same procedure as that described for the isolation of **6f** was used. A white glass was obtained which was dissolved in ethyl acetate. A white amorphous solid, 0.1 g, mp 170–175°, precipitated slowly. The product was purified by dissolving in hot ethyl acetate. A white amorphous solid (60 mg), mp 175–176°, $[\alpha]^{26}D$ + 10.5° (*c* 0.3, water), precipitated. The product exhibited essentially the same ultraviolet spectral data in water, acid, and base as **6b**. Paper chromatography in systems A and B showed one fluorescent spot with R_f 0.85 and 0.70, respectively (nucleoside **6b**, R_f 0.59 and 0.62].

Deacetylation of **6g** occurred readily in alkali. On the addition of 1 *N* sodium hydroxide to the *O*-acetate **6g**, the nucleoside **6b** precipitated immediately. This product had the same melting point and ultraviolet and infrared data as an authentic sample of **6b**. Chromatographic analysis of the filtrate showed that **6b** was the only product.

Anal. Calcd for $C_{13}H_{17}N_3O_4$: C, 55.90; H, 6.14; N, 15.05. Found: C, 55.95; H, 6.06; N, 15.14.

2,3′-Acetylaminoimino-1-(5-*O*-acetyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6i).—To 2,3′-aminoimino **6d** (0.1 g, 0.42 mmol) suspended in pyridine (15 ml) was added acetic anhydride (1.1 mmol). The reaction mixture was stirred at room temperature for 18 hr. The same procedure used in the isolation of the monoacetate **6f** was followed. A white glass was obtained which was dissolved in ethyl acetate. White prisms (76 mg), mp 253–257° (prior darkening), crystallized. Recrystallization of **6i** gave 54 mg, mp 257–262° (prior darkening), $[\alpha]^{25}D$ −84° (*c* 0.4, water). The ultraviolet absorption spectrum in water showed a maximum at 223 mμ (ε 17,350) and an inflection at 260 mμ (ε 4700). The 3-ml aqueous aliquot was acidified with 1 *N* hydrochloric acid, and then made basic with 1 *N* sodium hydroxide. The ultraviolet spectrum in acid showed a maximum at 224 mμ and a broad shoulder centered at 257 mμ. The spectrum in alkali showed a maximum at 240 mμ and a shoulder centered at 268 mμ. Paper chromatography of **6i** in systems A and B showed one ultraviolet absorbing spot with R_f 0.82 and 0.69, respectively (nucleoside **6d**, R_f 0.45 and 0.44).

Anal. Calcd for $C_{14}H_{18}O_5N_4$: C, 52.17; H, 5.63; N, 17.89. Found: C, 52.22; H, 5.54; N, 16.79.

2,3′-Hyroxyimino-1-(5-*O*-acetyl-2-deoxy-β-D-*threo*-pentofuranosyl)thymine (6h).—To 2,3′-hydroxyimino **6c** (0.1 g, 0.42 mmol) suspended in pyridine (15 ml) was added acetic anhydride (1.1 mmol). The reaction mixture was heated at 75° for a few hours until solution occurred and then allowed to stand overnight at room temperature. The same procedure as that described for the isolation of **6f** was used. A white glass (containing residual acetic acid) was obtained. The ultraviolet spectrum of the glass in water had a maximum at 224 mμ and an inflection at 255 mμ. In acid the spectrum had a maximum at 224 mμ and a broad inflection at 245–255 mμ. This pattern changed within 1.5 hr to one similar to **6c** at pH 0 (Table II). The data suggest that the glass contained mainly an unstable diacetate of **6c** with similar chemical properties to those observed for diacetate **6j**. The diacetate of **6c** was converted into the monoacetate **6h** under the following conditions. The glass was dissolved in ethanol and the solution was allowed to stand overnight at room temperature. Short white needles (72 mg), mp 214–219° dec (prior darkening), crystallized. Recrystallization from ethanol yielded 40 mg, mp 222–227° dec (with effervescence, prior darkening), $[\alpha]^{25}D$ +9° (*c* 0.5, water). Compound **6h** exhibited essentially the same ultraviolet spectral data in water, acid, and base as **6c** (Table II). Paper chromatography of **6h** in systems A and B showed one ultraviolet absorbing spot with R_f 0.76 and 0.59, respectively (nucleoside **6c**, R_f 0.42 and 0.46).

Anal. Calcd for $C_{12}H_{15}O_6N_3$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.27; H, 5.56; N, 14.76.

2-*N*-Acetyl-1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)isocytosine (11).—To isocytosine nucleoside **10** (0.4 g, 1.6 mmol) suspended in pyridine (20 ml) was added acetic anhydride (8.2 mmol). The reaction mixture was heated at 55° for 1 hr and then allowed to stand at room temperature overnight. Almost complete solution had occurred. Some starting material (~10 mg) was removed by filtration. Ethanol (0.2 ml) was added and the pyridine was evaporated *in vacuo*. A syrup was obtained. Upon dissolving the syrup in ethanol, white crystals (0.5 g, mp 106–110°) appeared. A small sample, on recrystallization from water, afforded prisms, mp 108–110°, $[\alpha]^{25}D$ +89° (*c* 0.4, water). Ultraviolet absorption properties in water were maxima at 256 mμ (ε 17,200) and 217 mμ (ε 10,800), and a minimum at 234 mμ (ε 7200). Compound **11** was unstable in acid and alkali and was converted into 1-β-D-arabinofuranosyluracil or an acetyl derivative thereof (see below).

Anal. Calcd for $C_{17}H_{21}N_3O_9$: C, 49.64; H, 5.15; N, 10.21. Found: C, 48.96; H, 5.19; N, 10.28.

Hydrolysis of the Tetraacetate 11. A. In Acid.—The tetraacetate **11** (0.1 g) dissolved in 0.08 *N* sulfuric acid (25 ml) was allowed to react for 3 hr at room temperature. During this time the ultraviolet spectra of the reaction mixture changed to that of arabinofuranosyluracil (**13**). The acid solution was neutralized with barium carbonate, and the resulting filtrate was evaporated to dryness. On the addition of ethanol to the residue, triacetate **12** precipitated. The yield of **12** was 36%, mp 127–128° (lit.[7] mp 129–130°). The ir, pmr, and analytical data of the triacetate were identical with those of an authentic sample of **12**.

(27) The fast-moving diacetate of **6j** spot was eluted with water. The ultraviolet spectrum of the solution had a maximum at 230 mμ, and a shoulder at 255 mμ. On the addition of acid to the solution, the spectrum changed (2–3 hr) to the acid spectrum of **6a** (Table II). Upon the addition of base to the aqueous solution of **6j** the spectrum immediately changed to that of **6a**.

B. In Alkali.—The tetraacetate 11 (25 mg) dissolved in 1 *N* sodium hydroxide (3 ml) was allowed to stand overnight at room temperature. During this time the ultraviolet spectra of the reaction mixture changed to that of arabinosyluracil (**13**). The basic solution was treated with Dowex 50 resin (H^+ form) and the resulting filtrate was subjected to chromatographic analysis using systems A and B. Only one ultraviolet absorbing spot corresponding to **13** was detected.

Reactions of 2,3′-Aminoimino Nucleoside 6d. A. Reaction with Nitrous Acid.—The 2,3′-aminoimino nucleoside **6d** (50 mg, 0.21 mmol) was dissolved in 70% acetic acid (3 ml). The solution was cooled, sodium nitrite (19 mg) in water (1 ml) was slowly added, and the reaction mixture was allowed to stand for 1 hr. The imino nucleoside **6a** was purified by absorption on a column of Dowex 50 (H^+, 100–200 mesh). The nucleoside was eluted with 2 *N* NH_4OH, and the ultraviolet absorbing eluate was evaporated *in vacuo* to dryness. The product was crystallized from ethanol. Compound **6a** (16 mg), mp 250° (sintering) and 268° (dec with effervescence), was obtained.

B. Reaction with Benzaldehyde.—A mixture of the 2,3′-aminoimino derivative **6d** (0.2 g, 0.84 mmol), benzaldehyde (0.2 ml), ethanol (10 ml), and three drops of concentrated hydrochloric acid was refluxed for 15 min. The solution was cooled, and concentrated ammonium hydroxide was added until a pH of about 8 was reached. Evaporation of the ethanol afforded a yellowish residue. The residue was first triturated with ether and then water was added. A white solid (**6e**) precipitated and was filtered. The solid was crystallized from ethanol. The benzal compound **6e** was obtained as white rodlike crystals (0.12 g, 44%), mp 258–292° dec (with effervescence). Ultraviolet absorption properties in ethanol were maxima at 308 and 228 mμ, inflections at 314 and 246 mμ, and a minimum at 269 mμ.

Anal. Calcd for $C_{17}H_{18}N_4O_8$: C, 62.57; H, 5.56; N, 17.17. Found: C, 62.43; H, 5.53; N, 17.23.

Stability of the Imino Bridge. In Alkali.—The 2,3′-imino compound (**6a**, 50 mg) was dissolved in 15 ml of 1 *N* NaOH. After standing 1 day at room temperature the ultraviolet absorption spectrum remained unchanged. The solution was placed on a Dowex 50 resin (H^+) and elution with 0.1 *N* NH_4OH followed by evaporation afforded 20 mg of crystals, mp 258–261° dec. The ir and chromatographic properties were identical with those obtained from **6a**.

Solutions of **6a** or **6b** in 7 *N* KOH for 3 weeks did not alter the uv spectra. (The uv spectrum of **6b** in 7 *N* KOH was identical with the uv spectrum in pH 6.92 solution except that the maximum at 228 mμ was masked by buffer absorption.)

In Acid.—The 2,3′-imino derivatives **6a–d** were more stable in aqueous acid than the "oxygen isostere" **2** or the uncyclized 2-amino nucleoside **9**.[8]

A paper chromatogram of the derivatives **6a–d**, **2**, and 2-deoxyribose was developed using a butanol–water system (84:14), and then spraying with acid cysteine reagent.[28] Only the 2,3′-anhydro nucleoside **2** (R_f 0.37) and 2-deoxyribose (R_f 0.32) gave the characteristic pink color with the cysteine reagent. The nucleosides **6a–d** were visualized using uv determinations and gave R_f 0.35, 0.48, 0.29, and 0.28 respectively.

The imino derivative **6a** (8.85 mg) was refluxed in 0.1 *N* hydrochloric acid (10 ml). An aliquot (0.05 ml) was removed and added to 5 ml of buffer (pH 7, pH 12, and pH 0) the ultraviolet spectrum was taken. After 1.1 hr, the spectra at these pHs were almost the same as those reported in Table II. [A small increase (6%) in absorption in the 260-mμ region was observed at pH 12]. After 22 hr, the spectra had changed appreciably: at pH 7, maxima at 214–218 mμ (ε 22,000), 270 (4000), and 302 (4300), minima of 257 mμ (ε 3800) and 282 (3700); at pH 12, maxima at 220 mμ (ε 21,400) and 275 (5000) and a shoulder at 300–310 (3000), minimum at 256 mμ (ε 3900); at pH 0, maxima at 227 mμ (ε 13,600) and 267 (9300), minimum at 249 mμ (ε 7300). After refluxing for 2 days, the uv spectra at pH 0 and 7 were essentially the same as the spectra after 1 day. At pH 12 there was a broad maximum between 275 and 302 mμ in addition to the maximum at 220 mμ. The above spectral changes indicate that some glycosyl cleavage had occurred. The 22-hr spectral patterns bore some resemblance to the spectral patterns of 5-methylisocytosine. 5-Methylisocytosine has been prepared previously[8] from 1-β-D-arabinofuranosyl-5-methylisocytosine (**9**). 5-Methylisocytosine had ultraviolet absorptions at λ_{max}^{water} 205 mμ (ε 7700) and 263 (2900), shoulders at 215 and 286; λ_{min} 246 (2300); $\lambda_{max}^{pH\ 12}$ 228 (4350) and 279 (3800); λ_{min} 220 (4130) and 246 (2400); $\lambda_{max}^{1\ N\ HCl}$ 221 (5500) and 261 (4000); λ_{min} 242 (3100).

It is probable that the sugar moiety or a derivative thereof remains attached to the 2-amino group thus accounting for the different spectral characteristics of the acid hydrolysate of **6a** and 5-methylisocytosine.

Registry No.—**2**, 15981-92-7; **4**, 15981-78-9; **6a**, 15981-79-0; **6b**, 15981-80-3; **6c**, 15981-81-4; **6d**, 15981-82-5; **6e**, 15981-83-6; **6f**, 16031-78-0; **6g**, 15981-84-7; **6h**, 15981-85-8; **6i**, 16065-64-8; **7**, 15981-86-9; **8**, 15981-87-0; **9**, 10212-31-4; **10**, 10212-30-3; **11**, 15981-93-8; **12**, 14057-18-2; 5-methylisocytosine, 15981-91-6.

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The Synthesis and Reactions of Some 8-Substituted Purine Nucleosides[1]

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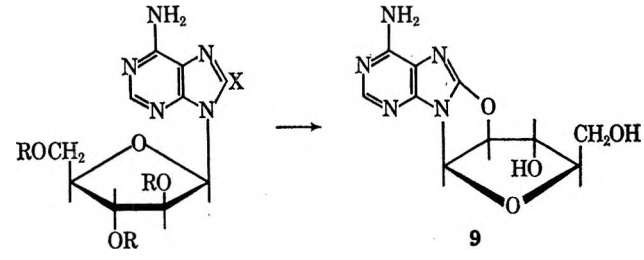
The preparation of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**3**) was accomplished by the bromination of 9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**2**). The reaction of **3** with basic nucleophiles such as sodium methoxide and ammonia effected an intramolecular displacement of bromide to give 8,2′-anhydro-8-hydroxy-9-(β-D-arabinofuranosyl)adenine (**9**). Displacement of the bromine of **3** by the nonbasic nucleophiles, thiourea and sodium azide, gave the 8-thiol and 8-azide. A similar set of reactions was carried out starting from 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**12**). The displacement of bromide from 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**13**) by both neutral and basic nucleophiles proceeded normally to give the appropriate 8-substituted purine xylofuranoside. There was no evidence for an intramolecular displacement of bromide to give 8,3′-anhydro nucleosides.

Enzymic hydroxylation of 6-methylthiopurine by hepatic aldehyde oxidase to give 6-methylthio-8-hydroxypurine was described in a recent paper.[2] It was suggested that such a mechanism may contribute significantly to the rapid biological inactivation of 6-methylthiopurine in the intact animal. On the basis of such a rationale, it might be expected that properly chosen 8-substituted derivatives of biologically active nucleosides can not be inactivated in this fashion, and hence may prove to be more satisfactory than the parent compound. 8-Aminoadenosine has been reported to be an effective inhibitor of *Streptococcus faecalis* (8043) and sarcoma S-180 ascites cells although it caused only slight inhibition of leukemia L-1210.[3] In view of the observed biological activity of 9-(β-D-arabinofuranosyl)adenine[4] (**1**) and 9-(β-D-xylofuranosyl)adenine[5] (**11**), it was of interest to prepare a series of 8-substituted derivatives of these compounds.

A number of papers have appeared recently which describe the facile preparation of 8-substituted purines and the corresponding nucleosides and nucleotides[6,7] by way of bromination of the 8 position of the adenine or guanine derivative. Displacement of the 8-bromo group by the appropriate nucleophile gave a variety of 8-substituted nucleosides. Such a general procedure appeared to offer a useful route for the preparation of the desired xylose and arabinose nucleosides.[2]

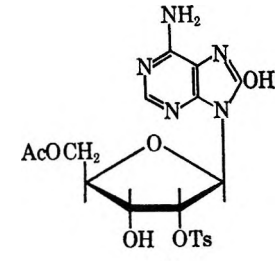
Acetylation of 9-(β-D-arabinofuranosyl)adenine[3] (**1**) at 0° gave crystalline 9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**2**). Bromination of **2** using N-bromoacetamide[6c] produced crystalline 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**3**) after purification *via* silica gel chromatography. Treatment of **3** with thiourea in ethanol[6c] displaced the bromine function to give 6-amino-9-(2,3,5-tri-O-acetyl-β-D-arabinosuranosyl)-9H-purine-8-thiol (**4**) as a crystalline solid which could be deacetylated easily to give 6-amino-9-(β-D-arabinofuranosyl)-9H-purine-8-thiol (**5**).

When the blocked bromo nucleoside (**3**) was treated with methanolic ammonia at room temperature as described by Holmes and Robins[6c] for the preparation of 8-bromoadenosine, the product isolated contained no bromine and had physical properties which were similar to those reported by Ikehara, *et al.*,[6a] for 8,2′-anhydro-8-hydroxy-9-(β-D-arabinofuranosyl)adenine (**9**) prepared from 6-amino-8-hydroxy-9-(5-O-acetyl-2-O-*p*-tolylsulfonyl-β-D-ribofuranosyl)-9H-purine (**10**).



1, R = H; X = H
2, R = Ac; X = H
3, R = Ac; X = Br
4, R = Ac; X = SH
5, R = H; X = SH
6, R = Ac; X = N_3
7, R = Ac; X = NH_2
8, R = H; X = NH_2

9



10

The anhydro nucleoside (**9**) was hydrolyzed using dilute aqueous sulfuric acid. The sugar obtained from this acid hydrolysis was identified as arabinose by paper chromatography. Thus, the anhydro nucleoside must have the 8,2′ structure (**9**).[9] This same anhydro nucleoside (**9**) was formed when the blocked bromo nucleoside (**3**) was treated with methanolic sodium methoxide in an attempt to prepare the 8-methoxyadenine arabinoside. Apparently basic nucleophiles such as sodium methoxide remove the O-acetates before any significant displacement of the bromine on C-8 occurs. The SN2 displacement is completely

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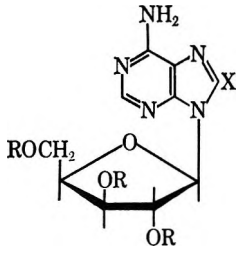
(9) Compound **9** was identical chromatographically and had an infrared spectrum similar to that of a sample of 8,2′-anhydro-8-hydroxy-9-(β-D-arabinofuranosyl)adenine which was kindly given to us by Dr. H. Tada.

overshadowed by the resulting intramolecular cyclization and anhydro nucleoside (**9**) is the sole product.

Neutral S_N2 reactions which do not remove the O-acetate proceed in a straightforward fashion. Thus, treatment of the bromotriacetate (**3**) with sodium azide in N,N-dimethylformamide (DMF) took place normally to give 8-azido-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**6**). Deacetylation of the blocked azide (**6**) to give the 8-azido-9-(β-D-arabinofuranosyl)-adenine failed. The product isolated was again the anhydro nucleoside (**9**). Although the blocked azide (**6**) was noncrystalline, spectral data, halogen analysis, and tlc data provided convincing proof that the anhydro nucleoside formed in this reaction did not come from unreacted 8-bromide (**3**) but must have come by the intramolecular displacement of the 8-azide by the sugar alkoxide, a somewhat surprising result for such mild conditions.

The preparation of 8-amino-9-(β-D-arabinofuranosyl)-adenine (**8**) was accomplished by hydrogenation of the blocked azide (**6**) to the blocked 8-amine (**7**) prior to deacetylation. Thus, the crystalline 8-amine (**8**) could be prepared in good yield.

By the same general procedure, 9-β-D-xylofuranosyladenine[10] (**11**) was acetylated, then brominated to give 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**13**) again purified by chromatography. The re-



11, R = X = H
12, R = Ac; X = H
13, R = Ac; X = Br
14, R = H; X = Br
15, R = Ac; X = SH
16, R = H; X = SH
17, R = H; X = OCH_3
18, R = H; X = N_3
19, R = H; X = NH_2

action of **13** with thiourea gave the syrupy 6-amino-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-9H-purine-8-thiol (**15**), which could be deacetylated to give crystalline 6-amino-9-(β-D-xylofuranosyl)-9H-purine-8-thiol (**16**). Treatment of the blocked 8-bromoxyloside (**13**) with either methanolic ammonia or methanolic sodium methoxide at room temperature gave a good yield of 8-bromo-9-(β-D-xylofuranosyl)adenine (**14**). There was no detectable evidence for any 8,3′-anhydro nucleoside formation. Treatment of either the 8-bromoxyloside (**14**) or its triacetate (**13**) with refluxing methanolic sodium methoxide gave 8-methoxy-9-(β-D-xylofuranosyl)adenine (**17**) again with no evidence for any 8,3′-anhydro nucleoside. The preparation of 8-azido-9-(β-D-xylofuranosyl)adenine (**18**) was accomplished by the displacement of 8-bromo-9-(β-D-xylofuranosyl)-adenine (**14**) by sodium azide in DMF. Hydrogenation of the azide gave 8-amino-9-(β-D-xylofuranosyl)-adenine (**19**).

(10) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

The failure to obtain any 8-3′-anhydro-8-hydroxy-9-(β-D-xylofuranosyl)adenine from the 8-bromoxyloside (**14**) is somewhat surprising in view of the exceptional ease with which the 8-bromoarabinoside (**3**) and 8-azidoarabinoside (**6**) were converted into the 8,2′-anhydro nucleoside. The ease of formation of 8,2′-anhydroarabinoside using alkaline conditions compared with the failure to form an 8,3′-anhydroxyloside from the 8-bromoxyloside (**14**) was also indicated during the measurement of the ultraviolet spectra of **3** and **14**. Thus, the 8-bromoxyloside (**14**) has a band at $\lambda_{max}^{pH\ 13}$ 265 mμ (ε 16,700). Holmes and Robins[6b] report a band at $\lambda_{max}^{pH\ 11}$ 264 mμ (ε 17,600) for 8-bromoadenosine. The 8-bromoarabinoside (**3**) on the other hand had an absorption at $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 13,380), a value which indicated a significant conversion into the 8,2′-anhydroarabinoside (**9**).

Examination of molecular models gives no indication of any steric problem to account for the failure to form the 8,3′-anhydro bond. The chemistry of anhydro nucleosides in the pyrimidine series showed similar results. Thus 2,2′-anhydro nucleosides were formed inevitably in preference to 2,3′-anhydro nucleosides,[11] although 2,3′-anhydro nucleosides have been prepared.[12a] The "up" 2′-hydroxyl of arabinopyrimidine nucleosides is reported to attack the pyrimidine C-6, whereas the up 3′-hydroxyl of 2′-deoxyxylopyrimidine nucleosides does not.[12b]

Experimental Section[13]

9-(2,3,5-Tri-O-acetyl-β-D-arabinofuranosyl)adenine (2).—A suspension of 2.5 g (9.36 mmol) of 9-(β-D-arabinofuranosyl)-adenine (**1**) and 4.6 ml (48.8 mmol) of acetic anhydride in 35 ml of dry pyridine was stirred at 0° under a nitrogen atmosphere for 19 hr, then the excess acetic anhydride was decomposed by the addition of 2 ml of ethanol. The decomposed mixture was stirred for 1 hr at 0°, then was evaporated to dryness *in vacuo*. The residue was dissolved in 40 ml of chloroform and washed with 15 ml each of water, saturated aqueous sodium bicarbonate, and water; then it was dried and evaporated to dryness *in vacuo* to give 3.26 g of product as an orange gum. Two recrystallizations from ethanol gave 1.26 g (34%) of white crystals: mp 128.5–129.0°; $[\alpha]^{22}D$ −13° (*c* 0.74, chloroform); $\lambda_{max}^{ethanol}$ 259 mμ (ε 14,200).

Anal. Calcd for $C_{16}H_{19}N_5O_7$: C, 48.9; H, 4.87; N, 17.8. Found: C, 48.7; H, 4.61; N, 17.5.

8-Bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (3).—A mixture of 3.15 g (8.0 mmol) of 9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**2**) and 3.5 g (22.4 mmol) of N-bromoacetamide in 50 ml of chloroform, which had been dried over sulfuric acid, was heated at reflux with stirring while protected from moisture for 15 hr, then was evaporated to dryness *in vacuo*. The residue was partitioned between 50 ml each of ethyl acetate and 10% aqueous sodium hydrosulfite. The organic layer was washed with 10 ml of water, then was dried and evaporated to dryness *in vacuo*. The residue was dissolved in chloroform, then was applied to a column of silica gel (450 g, 4.9 × 47 cm). Elution with chloroform (500 ml) then ethyl

(11) (a) D. M. Brown, D. B. Parihar, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958); (b) N. C. Yung and J. J. Fox, *J. Amer. Chem. Soc.*, **83**, 3060 (1961); (c) T. Naito, M. Hirata, Y. Nakai, T. Kobayashi, and M. Kanao, *Chem. Pharm. Bull.* (Tokyo), **13**, 1258 (1965).

(12) (a) J. F. Codington, R. Fecher, and J. J. Fox, *J. Amer. Chem. Soc.*, **82**, 2794 (1960); (b) J. J. Fox, N. C. Miller, and R. J. Cushley, *Tetrahedron Lett.*, 4927 (1966).

(13) Melting points are corrected. Thin layer chromatograms were run on silica gel HF (E. Merck A-G Darmstadt). Paper chromatograms were run on Whatman No. 1 paper by the descending technique. Spots were detected by visual examination under an ultraviolet lamp for the nucleosides. Reducing sugars were detected by aniline citrate. The solvent systems used were solvent A, chloroform–methanol (9:1); solvent B, absolute ethanol; solvent C, 65% aqueous 2-propanol–ethyl acetate (35:65).

acetate–chloroform (500 ml of 1:3 then 1 l. of 3:1) removed some impurities. Elution with an additional 1 l. of ethyl acetate–chloroform (3:1) and finally 4 l. of ethyl acetate gave a total of 1.01 g (36%) of **3** as pale orange needles: mp 178.5–179.0°; $[\alpha]^{22}D$ −73° (*c* 0.4, chloroform); $\lambda_{max}^{pH\ 1}$ 262 mμ (ε 17,250); $\lambda_{max}^{pH\ 7}$ 263 mμ (ε 15,400); $\lambda_{max}^{pH\ 13}$ 260 mμ (ε 13,380).

Anal. Calcd for $C_{16}H_{18}BrN_5O_7$: C, 40.7; H, 3.82; Br, 16.9; N, 14.9. Found: C, 40.7; H, 3.98; Br, 16.6; N, 14.5.

6-Amino-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)-9H-purine-8-thiol (4).—A solution of 614 mg (1.3 mmol) of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**3**) and 135 mg (1.77 mmol) of thiourea in 30 ml of ethanol was stirred at reflux under nitrogen for 18 hr, then was evaporated to dryness *in vacuo*. The residue was partitioned between 30 ml of chloroform and 10 ml of water. The organic phase was dried, then evaporated to dryness *in vacuo* to give crude product as a yellow foam. This material was dissolved in chloroform and applied to a column of silica gel (55 g, 1.4 × 36 cm). After elution of some by-products using chloroform (425 ml) and 10% ethyl acetate in chloroform (500 ml), product was eluted using ethyl acetate–chloroform (1:1, 800 ml) and 100% ethyl acetate. The residue from these last fractions was a white foam weighing 365 mg (86%). Crystallization was effected by dissolving the foam in ethanol then allowing the solvent to evaporate to give material with mp 176.5–179.5°; $[\alpha]^{21}D$ −39° (*c* 0.40, chloroform); $\lambda_{max}^{pH\ 1}$ 308 mμ (ε 23,200), 243 (9360), 222 (12,600); $\lambda_{max}^{pH\ 7}$ 297 mμ (ε 21,900), 227 (18,300); $\lambda_{max}^{pH\ 13}$ 297 mμ (ε 21,000).

Anal. Calcd for $C_{16}H_{19}N_5O_7S \cdot C_2H_5OH$: C, 45.9; H, 5.35; N, 14.9; S, 6.80. Found: C, 45.8; H, 5.13; N, 14.7; S, 6.97.

The nmr spectrum contained a triplet at τ 8.75 and a quartet at 6.24, thus demonstrating the presence of ethanol.

6-Amino-9-(β-D-arabinofuranosyl)-9H-purine-8-thiol (5).—A solution of 234 mg (0.55 mmol) of 6-amino-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)-9H-purine-8-thiol (**4**) and 33 mg (0.61 mmol) of sodium methoxide in 15 ml of methanol was stirred at room temperature under a nitrogen atmosphere for 15 hr. The solution was neutalized with 2 drops of glacial acetic acid, then evaporated to dryness *in vacuo*. The residue was purified by means of the lead salt[14] to give 96 mg (60%) of product as a white solid. Recrystallization from methanol gave 74 mg (45%) of white needles: mp 199.5–202.5°; $[\alpha]^{22}D$ 9° (*c* 0.40, methanol); $\lambda_{max}^{pH\ 1}$ 308 mμ (ε 22,600), 242 (10,500), 222 (11,700); $\lambda_{max}^{pH\ 7}$ 302 mμ (sh, ε 21,500), 297 (22,000), 228 (17,500); $\lambda_{max}^{pH\ 13}$ 296 mμ (ε 21,200).

Anal. Calcd for $C_{10}H_{13}N_5O_4S \cdot 0.6H_2O$: C, 38.7; H, 4.62; N, 22.6; S, 10.3. Found: C, 39.0; H, 4.92; N, 22.2; S, 10.4.

A thiol titration consumed 93% (based on 0.6 H_2O) of the theoretical uptake of iodine.

8,2′-Anhydro-8-hydroxy-9-(β-D-arabinofuranosyl)adenine (9).—A solution of 0.5 g of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**3**) in 15 ml of methanol which had been saturated previously with anhydrous ammonia at 0° was kept at room temperature in a Parr bomb for 32 hr. The reaction was cooled to 0° then filtered to give 158 mg of pink crystals. Recrystallization from water gave 117 mg (42%) of product: mp 212.0–212.5° dec; $[\alpha]^{23}D$ −108° (*c* 0.30, pyridine); $\lambda_{max}^{pH\ 1}$ 259 mμ (ε 12,900); $\lambda_{max}^{pH\ 7}$ 255 mμ (ε 13,100); $\lambda_{max}^{pH\ 13}$ 259 mμ (ε 12,700).

The nmr spectrum had a band at δ 6.42 (J = 5 cps) assigned to H′-1.

Anal. Calcd for $C_{10}H_{11}N_5O_4 \cdot 0.2H_2O$: C, 44.7; H, 4.27; N, 26.0. Found: C, 44.4; H, 4.14; N, 26.2.

Ikehara, *et al.*,[6a] report mp >190° dec; $[\alpha]^{19}D$ −122° (*c* 0.75, pyridine); $\lambda_{max}^{pH\ 1}$ 260 mμ (ε 10,800); $\lambda_{max}^{H_2O}$ 260 mμ (ε 11,000); $\lambda_{max}^{pH\ 14}$ 260 mμ (ε 10,700). The nmr spectrum had a band at δ 6.50 (J = 5.4 cps) which he assigned to H′-1.

A 50-mg sample of the cyclonucleoside **9** was heated at reflux for 8 hr with 8 ml of 0.1 *N* sulfuric acid. The reaction was cooled to room temperature and neutralized with Amberlite IR-45 (OH^-) to pH 7. Paper chromatography of the product, using solvent C as the developing solvent, showed one spot at R_{ribose} 0.69 that gave a positive test for reducing sugar with aniline citrate. D-Arabinose had a spot at R_{ribose} 0.69; D-xylose had a spot at R_{ribose} 0.84.

8-Amino-9-(β-D-arabinofuranosyl)adenine (8).—To a solution of 3.0 g (6.34 mmol) of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**3**) in 28 ml of dry DMF was added 1.32 g (20 mmol) of sodium azide. The resulting solution was stirred at 75° for 10 hr, then was evaporated to dryness *in vacuo*. The residue was partitioned between 20 ml each of dichloromethane and water. The organic layer was dried then evaporated to dryness *in vacuo* to give 2.9 g of crude 8-azido-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**6**) as a syrup: λ_{max}^{film} 4.6 μ (N_3); $\lambda_{max}^{pH\ 1}$ 279 mμ (ε 15,600); $\lambda_{max}^{pH\ 13}$ 264 mμ (ε 11,400).

Thin layer chromatography using solvents A and B showed one main spot with R_f 0.61 and 0.53, respectively. There were two trace components with slower R_f values. Bomine analysis showed 1.44% Br indicating a maximum of 8.5% starting material.

A solution of 1.98 g (4.56 mmol) of crude 8-azido-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**6**) in 250 ml of 95% ethanol was hydrogenated at room temperature for 15 hr using 1 g of 5% palladium on charcoal. The mixture was filtered through a Celite pad and the filtrate was evaporated to dryness *in vacuo* to give 1.76 g of 8-amino-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**7**) as a yellow foam. There was no azide absorption at 4.6 μ. Tlc using solvents A and B showed one spot with R_f values of 0.26 and 0.32, respectively.

Treatment of 1.49 g of 8-amino-9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**7**) with methanolic sodium methoxide at 0° for 3 days caused the precipitation of 0.66 g of 8-amino-9-(β-D-arabinofuranosyl)adenine (**8**). The mother liquors after the removal of crystalline **8** were neutralized and worked up in the usual fashion to give an additional 0.2 g of crystalline product. The fractions were combined and recrystallized from 80% aqueous ethanol to give 0.71 g (54% over-all yield from **3**) of crystals, mp 142–145°, which resolidified and remelted at 237.5–240° dec.

The analytical sample [dried at 100° (1 mm) for 16 hr] had mp 142.5–146°, resolidifing and remelting at 238–240° dec. It was redried at 152° (1 mm) for 2 hr and had mp 239–241° dec; $[\alpha]^{22}D$ +10° (*c* 1.0, 2-methoxyethanol); $\lambda_{max}^{pH\ 1}$ 269 mμ (ε 13,500); $\lambda_{max}^{pH\ 7}$ 273 mμ (ε 16,600); $\lambda_{max}^{pH\ 13}$ 275 mμ (ε 16,800).

Anal. Calcd for $C_{10}H_{14}N_6O_4$: C, 42.6; H, 5.00; N, 29.8. Found: C, 42.7; H, 5.21; N, 29.6.

9-(2,3,5-Tri-O-acetyl-β-D-xylofuranosyl)adenine (12).—Acetylation of 12.0 g (45 mmol) of 9-(β-D-xylofuranosyl)adenine (**11**)[9] in 285 ml of pyridine using 13.1 ml (128 mmol) of acetic anhydride was carried out as described for the preparation of 9-(2,3,5-tri-O-acetyl-β-D-arabinofuranosyl)adenine (**2**) to give 15.5 g (88%) of **12** as a white foam: $[\alpha]^{24}D$ −14° (*c* 0.56, chloroform); $\lambda_{max}^{pH\ 1}$ 256 mμ (ε 14,750); $\lambda_{max}^{pH\ 7}$ 258 mμ (ε 14,750); $\lambda_{max}^{pH\ 13}$ 256 mμ (ε 18,200).

Anal. Calcd for $C_{15}H_{19}N_3O_7 \cdot {}^1/_2H_2O$: C, 47.8; H, 5.01; N, 17.4. Found: C, 47.6; H, 5.05; N, 17.4.

8-Bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (13).—A solution of 2.0 g of 9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-adenine (**12**) in 20 ml of dichloromethane was dried by the azeotropic distillation of 10 ml of the solvent. The dry solution was added to a stirred suspension of 2.5 g (17.4 mmol) of N-bromoacetamide in 350 ml of dry carbon tetrachloride. The reaction was stirred under reflux for 16 hr while protected from moisture, then it was evaporated to dryness *in vacuo*. The residue was dissolved in 50 ml of chloroform–ethyl acetate (1:1) and was extracted with 25 ml each of 10% aqueous sodium bisulfite, saturated aqueous sodium bicarbonate, and water; then it was dried and evaporated to dryness *in vacuo* to give 2.53 g of an orange gum. The crude product was dissolved in 10 ml of chloroform and applied to a column of silica gel (300 g, 1.5 × 30 cm). The column was eluted with ethyl acetate–chloroform (3:1) until all uv-absorbing by-products were eluted (*ca.* 3 l.). Finally elution with ethyl acetate gave 2.0 g (83%) of **13** as a yellow foam. Further elution with ethyl acetate–methanol gave varying amounts of starting material (**12**).

The analytical sample of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**13**) from the column was homogeneous on tlc using ethanol as the developing agent and had a spot at R_f 0.6; $[\alpha]^{25}D$ −8° (*c* 0.4, methanol); $\lambda_{max}^{pH\ 1}$ 263 mμ (ε 17,400); $\lambda_{max}^{pH\ 7}$ 265 mμ (ε 15,700); $\lambda_{max}^{pH\ 13}$ 265 mμ (ε 16,000).

Anal. Calcd for $C_{16}H_{18}BrN_5O_7$: C, 40.7; H, 3.82; Br, 16.9; N, 14.9. Found: C, 40.8; H, 3.88; Br, 16.9; N, 14.5.

8-Bromo-9-(β-D-xylofuranosyl)adenine (14).—A solution of 250 mg of purified 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**13**) in 20 ml of methanol in a Parr bomb was cooled to 0° and saturated with gaseous ammonia. The reaction was kept at room temperature for 16 hr, then it was evaporated to

(14) E. J. Reist and L. Goodman, *Biochemistry*, **3**, 15 (1964).

dryness *in vacuo*. The solid residue was recrystallized from water to give 135 mg (74%) of crystalline product, mp 197.5–198.0°.

The analytical sample had mp 194.5–195.5°; $[\alpha]^{25}D$ −46° (*c* 0.5, methanol); $\lambda_{max}^{pH\ 1}$ 263 mμ (ε 17,700); $\lambda_{max}^{pH\ 7,\ 13}$ 265 mμ (ε 16,700).

Anal. Calcd for $C_{10}H_{12}BrN_5O_4 \cdot {}^1/_4H_2O$: C, 34.3; H, 3.59; Br, 22.8; N, 20.0. Found: C, 34.3; H, 4.05; Br, 22.8; N, 20.0.

6-Amino-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-9H-purine-8-thiol (15).—A solution of 5.47 g (11.6 mmol) of 8-bromo-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)adenine (**13**) and 1.2 g (15.8 mmol) of thiourea in 200 ml of absolute ethanol was heated at reflux under a nitrogen atmosphere for 5 hr. The yellow solution was evaporated to dryness *in vacuo* and the residue was partitioned between 15 ml of water and 50 ml of chloroform. The chloroform layer was dried and evaporated to dryness *in vacuo* to give 5.2 g of crude blocked thiol (**15**) as a yellow foam. A solution of crude **15** in chloroform was chromatographed on 150 g of silica gel. After elution with dichloromethane to remove by-products, elution with ethyl acetate gave 2.96 g (66%) of **15** as a yellow gum: $[\alpha]^{23}D$ −6° (*c* 0.5, chloroform); $\lambda_{max}^{pH\ 1}$ 307.5 mμ (ε 24,800), 242 (10,000); $\lambda_{max}^{pH\ 7,\ 13}$ 297 mμ (ε 22,500).

Anal. Calcd for $C_{16}H_{19}N_5O_7S$: C, 45.2; H, 4.50; N, 16.5; S, 7.54. Found: C, 44.6; H, 4.38; N, 15.9; S, 7.33.

6-Amino-9-(β-D-xylofuranosyl)-9H-purine-8-thiol (16). **A.**—Deacetylation of 1.38 g (3.24 mmol) of 6-amino-9-(2,3,5-tri-O-acetyl-β-D-xylofuranosyl)-9H-purine-8-thiol (**15**) was carried out using 193 mg (3.56 mmol) of sodium methoxide in 45 ml of methanol in the manner described for the deacetylation of the arabinoside (**5**). After purification by means of the lead salt, 540 mg of crude product was obtained as a yellow gum. Crystallization was accomplished by dissolving the gum in 8 ml of methanol and diluting with 20 ml of acetonitrile. On cooling 333 mg (34%) of product was obtained: mp 238–239° dec; $[\alpha]^{21}D$ −69° (*c* 0.4, methanol); $\lambda_{max}^{pH\ 1}$ 308 mμ (ε 24,500), 245 (11,150); $\lambda_{max}^{pH\ 7,\ 13}$ 297 mμ (ε 23,200).

Anal. Calcd for $C_{10}H_{13}N_5O_4S$: C, 40.1; H, 4.35; N, 23.4; S, 10.7. Found: C, 40.4; H, 4.44; N, 23.5; S, 10.4.

B.—A solution of 2.87 g (8.28 mmol) of 8-bromo-9-(β-D-xylofuranosyl)adenine (**14**) and 0.86 g (11.3 mmol) of thiourea in 150 ml of absolute ethanol was heated at reflux for 18 hr, then evaporated to dryness *in vacuo*. Purification, by means of the lead salt, then crystallization from methanol–acetonitrile (25 ml: 200 ml) gave 1.13 g (46%) of product, mp 230–232° dec, which was identical with material obtained in method A.

8-Methoxy-9-(β-D-xylofuranosyl)adenine (17).—A solution of 2.2 g (6.35 mmol) of crystalline 8-bromo-9-(β-D-xylofuranosyl)-adenine (**14**) and 1.21 g (22.3 mmol) of sodium methoxide in 100 ml of methanol was heated at reflux under a nitrogen atmosphere for 17 hr. The reaction was cooled to room temperature, neutralized with acetic acid, and evaporated to dryness *in vacuo*. Trituration of the residue with 10 ml of ice-cold water gave 1.43 g of crude product as a tan powder. Recrystallization from 40 ml of water gave 1.2 g (63%) of crystals: mp 197.5–199.0°; $[\alpha]^{23}D$ −63° (*c* 0 4, methanol); $\lambda_{max}^{pH\ 1}$ 261 mμ (ε 12,850); $\lambda_{max}^{pH\ 7,\ 13}$ 260 mμ (ε 13,650).

Anal. Calcd for $C_{11}H_{15}N_5O_5 \cdot {}^1/_5H_2O$: C, 43.9; H, 5.16; N, 23.3. Found: C, 44.2; H, 5.01; N, 22.9.

8-Azido-9-(β-D-xylofuranosyl)adenine (18).—To a solution of 2.76 g (7.98 mmol) of 8-bromo-9-(β-D-xylofuranosyl)adenine (**14**) in 35 ml of dry N,N-dimethylformamide was added 1.66 g of sodium azide. The resulting solution was stirred for 10 hr at 75°, then was evaporated to dryness *in vacuo*. The residue was triturated first with 30 ml of dichloromethane, then with 40 ml of water. The resulting residue was recrystallized from 60 ml of 95% aqueous ethanol to give 1.66 g (67%) of product: mp *ca.* 270° dec; $[\alpha]^{24}D$ −74° (*c* 0.5, 2-methoxyethanol); $\lambda_{max}^{pH\ 1}$ 281 mμ (ε 18,400); $\lambda_{max}^{pH\ 7}$ 281 mμ (ε 14,900); $\lambda_{max}^{pH\ 13}$ 280 mμ (ε 16,200).

Anal. Calcd for $C_{10}H_{12}N_8O_4$: C, 39.0; H, 3.92; N, 36.4. Found: C, 38.8; H, 4.22; N, 36.1.

8-Amino-9-(β-D-xylofuranosyl)adenine (19).—A suspension of 1.48 g (4.8 mmol) of 8-azido-9-(β-D-xylofuranosyl)adenine (**18**) and 1.0 g of 5% palladium on charcoal in 325 ml of water was stirred at room temperature under a hydrogen atmosphere for 15 hr. The mixture was filtered through a Celite pad, then the filtrate was evaporated to dryness *in vacuo* to give 0.7 g (52%) of product as a white solid, mp 150–153°. There was no absorption attributable to azide at 4.7 μ in the infrared.

Recrystallization from 98% aqueous ethanol gave the analytical sample: mp 155–160° dec; $[\alpha]^{22}D$ −51° (*c* 1.0, 2-methoxyethanol); $\lambda_{max}^{pH\ 1}$ 270 mμ (ε 13,400); $\lambda_{max}^{pH\ 7}$ 273 mμ (ε 16,430); $\lambda_{max}^{pH\ 13}$ 275 mμ (ε 16,400).

Anal. Calcd for $C_{10}H_{14}N_8O_4 \cdot 0.75H_2O$: C, 40.6; H, 5.28; N, 28.4. Found: C, 40.7; H, 5.37; N, 28.4.

Registry No.—**2**, 15830-52-1; **3**, 15830-53-2; **4**, 15830-54-3; **5**, 15830-55-4; **6**, 15830-56-5; **8**, 15830-57-6; **9**, 13089-44-6; **12**, 15830-77-0; **13**, 15830-59-8; **14**, 15830-78-1; **15**, 15830-60-1; **16**, 15830-61-2; **17**, 15830-79-2; **18**, 15830-80-5; **19**, 15830-62-3.

Acknowledgment.—The authors wish to thank Mr. O. P. Crews and his staff for the preparation of quantities of 9-(β-D-arabinofuranosyl)adenine and 9-(β-D-xylofuranosyl)adenine. They also wish to thank Dr. Peter Lim's group for the ultraviolet spectra and optical rotations.

Studies on Cyclic Polyols. XI. New Syntheses of Inosadiamines[1-3]

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DL-1,2-O-Isopropylidene-(1,2/5)-5-acetamido-3-cyclopentene-1,2-diol (**3**) has been prepared and has been converted, by permanganate hydroxylation and acetylation, into DL-1,2-di-O-acetyl-3,4-O-isopropylidene-(1,2,5/3,4)-5-acetamidocyclopentane-1,2,3,4-tetrol (**4a**). Selective removal of either the O-acetyl groups or the O-isopropylidene group converts **4a** into **5** and **6**, respectively, each of which is susceptible to glycol cleavage by periodate. Treatment of **5** with periodate produces DL-*lyxo*-4-acetamido-2,3-O-isopropylidenedioxypentanedial (**11**), whereas **6** is converted into DL-*ribo*-4-acetamido-2,3-diacetoxypentanedial (**17**). DL-1,2-Di-O-acetyl-(1,5/2)-5-acetamido-3-cyclopentene-1,2-diol (**8**) has been hydroxylated with permanganate to produce DL-3,4-di-O-acetyl-(1,2,4/3,5)-5-acetamidocyclopentane-1,2,3,4-tetrol (**10**). On treatment with periodate, **10** is converted into DL-*xylo*-4-acetamido-2,3-di-O-acetoxypentanediol (**21**). Treatment of the dialdehydes **11**, **17**, and **21** with nitromethane under alkaline conditions leads to the formation of mixtures of partially acetylated derivatives of acetamidonitrodideoxyinositols. By catalytic hydrogenation in the presence of Raney nickel T-4, followed by acetylation, the latter are converted into the corresponding diacetamidodideoxyinositols (inosadiamines). By chromatography on alumina, nine pure compounds were isolated and identified, of which six were previously unreported. From the *lyxo*-dialdehyde **11** four inosadiamine hexaacetates were obtained: 4,6-diacetamido-1,2,3,5-tetra-O-acetyl-4,6-dideoxy-*myo*-inositol (**13**); DL-2,6-diacetamido-1,3,4,5-tetra-O-acetyl-2,6-dideoxy-*epi*-inositol (**14**); DL-1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*allo*-inositol (**15**); and 1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*neo*-inositol (**16a**) or DL-2,4-diacetamido-1,3,5,6-tetra-O-acetyl-2,4-dideoxy-*chiro*-inositol (**16b**). The corresponding monoisopropylidene derivatives were obtained by a minor modification of the procedure; these were DL-4,6-diacetamido-1,5-di-O-acetyl-4,6-dideoxy-3,4-O-isopropylidene-*myo*-inositol (**13-Ip**); DL-2,6-diacetamido-1,3-di-O-acetyl-2,6-dideoxy-4,5-O-isopropylidene-*epi*-inositol (**14-Ip**); and DL-1,3-diacetamido-2,4-di-O-acetyl-1,3-dideoxy-5,6-O-isopropylidene-*neo*-inositol (**16-Ip-a**) or DL-2,4-diacetamido-1,3-di-O-acetyl-2,4-dideoxy-5,6-O-isopropylidene-*chiro*-inositol (**16-Ip-b**). From the *ribo*-dialdehyde **17** three inosadiamine hexaacetates were obtained: DL-2,6-diacetamido-1,3,4,5-tetra-O-acetyl-2,6-dideoxy-*epi*-inositol (**14**); DL-1,5-diacetamido-2,3,4,6-tetra-O-acetyl-1,5-dideoxy-*myo*-inositol (**19**); and 1,5-diacetamido-2,3,4,6-tetra-O-acetyl-1,5-dideoxy-*epi*-inositol (**20a**) or DL-1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*epi*-inositol (**20b**). From the *xylo*-dialdehyde **21** three previously known isomers were obtained: 1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*scyllo*-inositol (hexaacetyl streptamine, **23**); 1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*myo*-inositol (**24**); and DL-1,3-diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*chiro*-inositol (**25**). When ^{14}C-labeled nitromethane was used in the condensation reactions, ^{14}C-labeled **13**, **14**, **15**, **19**, **20**, **23**, and **24** were isolated.

Current interest in the chemistry of cyclohexane aminocyclitols is due largely to the occurrence of such substances as components of certain antibiotics.[2,5] The inosamines have been investigated in many laboratories and thirteen of the twenty theoretically possible isomers have been synthesized and characterized in the past twenty years. On the other hand, only ten of the fifty-four theoretically possible diasteroisomeric inosadiamines have been synthesized.[6-9] Our interest in this problem has come from synthetic studies in this laboratory[10,11] on cyclopentane aminocyclitols.

The present communication describes the synthesis of several isomeric inosadiamines, starting from cyclopentane aminocyclitols. Suitable derivatives of the 5-acetamido-3-cyclopentene-1,2-diols previously reported[11] have been converted into acetamidocyclopentanetetrols (see Chart I). Selective derivatization followed by periodate oxidation has yielded the corre-

(1) (a) Supported in part by U. S. Public Health Service Research Grants AM-07719 and GM-13971 from the National Institutes of Health. (b) The nomenclature of cyclitols has been unsettled, and many authors have devised their own systems for indicating configurational relationships (see ref 2 below). Recently an international committee under the auspices of IUPAC and IUB has recommended a set of rules for cyclitol nomenclature, based largely on proposals by Drs. S. J. Angyal and L. Anderson. These recommendations have been adopted as official, tentative rules by the IUPAC/IUB Commission on Biochemical Nomenclature and by the IUPAC Commission on Nomenclature of Organic Chemistry. The cyclitols described in the present study are named by the Angyal–Anderson system. The recommendations of the Joint Cyclitol Nomenclature Subcommittee provide that the basic method of naming and numbering cyclitols shall be the IUPAC Rules for Nomenclature of Organic Chemistry, Part C, as published in *Pure Appl. Chem.*, **11**, No. 1 and 2 (1965). Additional stipulations are then given to resolve questions of numbering preference which are unique to the cyclitols and related compounds, and a method for designating absolute configuration is provided. When the IUPAC organic chemistry rules are used, as with the cyclopentane derivatives discussed in this paper, relative configuration is indicated by a fractional prefix (Maquenne) in which the locants (positional numbers) of all the substituents on one side of the plane of the ring are arranged in ascending order in the numerator, and the locants for the substituents on the other side of the plane are in the denominator.

An exception to the IUPAC organic chemistry rules is made for compounds which may be considered to be derived from the inositols (cyclohexanehexols) by replacement of one or two of the hydroxyl groups by other univalent substituents. Such cyclitols are named as substituted inositols; the inosadiamines, for example, become *x,y*-diamino-*x,y*-dideoxyinositols. The relative configuration is designated by the prefix used for the parent inositol, and the positions are numbered as in the parent inositol. There are alternative ways of numbering each of the inositols, but replacement of $-OH$ by $-NH_2$ may eliminate some of the alternatives. The alternative used is the one which gives the amino groups the lower numbers; *e.g.*, in the present work (see Chart II) the amino groups of compound **15** are numbered 1,3 rather than 2,4 and the amino groups of compound **16a** are numbered 1,3 rather than 4,6. One new name must also be mentioned. The optically active and racemic inositols are now designated as D-, L- and DL-*chiro*-inositol, respectively. This name is used in the present work.

In the representation of the various compounds in the charts, the same enantiomer is not always shown. We feel that by showing the correct configurational relationships between starting material and products we will add to the clarity of the presentation.

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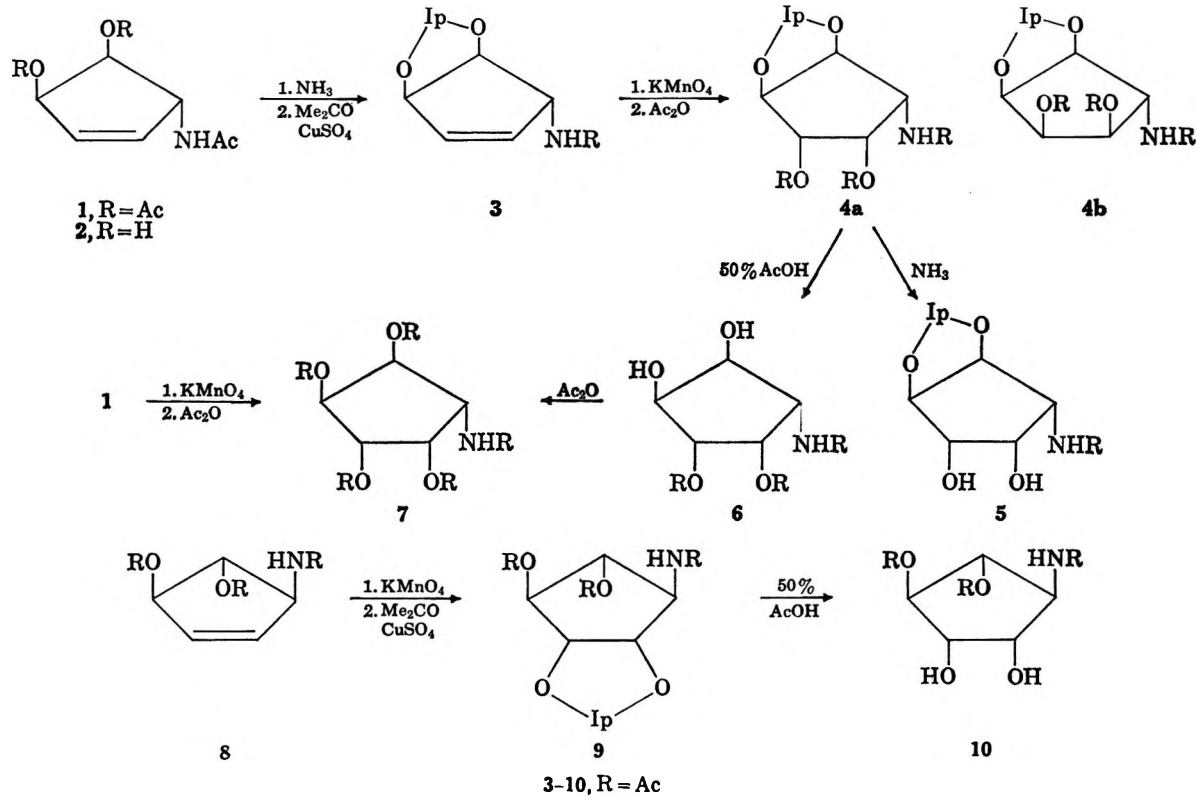
CHART I



sponding trisubstituted pentanedials. The latter compounds, on treatment with nitromethane[9d,e] followed by catalytic reduction and acetylation, gave mixtures of hexaacetyl *m*-inosadiamines. The mixtures were separated by chromatography and fractional crystallization. Configurational assignments are based on the known configuration of the starting materials and the chemical shifts of the methyl protons of the acetyl groups.[8,12-14] Altogether, nine inosadiamines (six of them previously unreported) have been characterized. Some of the syntheses were repeated with ^{14}C-labeled nitromethane, to give specifically labeled inosadiamines.

Results

Selectively Blocked Acetamidocyclopentanetetrols.—The 5-acetamido-3-cyclopentene-1,2-diols[11] **1** and **8** (Chart I) have yielded three different dialdehydes, as shown in Charts I and II. DL-1,2-di-O-acetyl-(1,2/5)-5-acetamido-3-cyclopentene-1,2-diol (**1**) was first transformed into the corresponding O-isopropylidene derivative **3**; hydroxylation with permanganate, and acetylation then gave a product which could have been either **4a** or **b**. However, by two reactions not involving the asymmetric centers the substance was converted into the known pentaacetate[11] **7**, and structure **4a** is therefore correct. Selective removal of either the O-acetyl groups or the O-isopropylidene group then gave, respectively, glycols **5** and **6**. In the case of the all-*trans* compound DL-1,2-di-O-acetyl-(1,5/2)-5-acetamido-3-cyclopentene-1,2-diol (**8**), a previous study[11] had shown that the di-O-acetylacetamidotetrol produced by treatment with permanganate was **10**. In order to obtain a pure sample of **10**, the syrupy crude product was converted into the crystalline O-isopropylidene derivative **9** which was purified and then hydrolyzed with 50% acetic acid to give **10**.

Treatment of the glycols with periodate converts **5** into DL-*lyxo*-4-acetamido-2,3-isopropylidenedioxypentanedial (**11**); **6** is converted into DL-*ribo*-4-acetamido-2,3-diacetoxypentanedial (**17**); and **10** is converted into DL-*xylo*-4-acetamido-2,3-diacetoxypentanedial (**21**) (see Chart II).

Inosadiamines from *lyxo* Dialdehyde 11.—Treatment of the dialdehyde **11** with nitromethane under alkaline conditions[9d] produced a mixture of stereoisomeric deoxynitroinosamines **12** (see Chart II). Attempted catalytic hydrogenation of **12** with PtO_2, Raney nickel (W-2), or 10% palladium on carbon, under various conditions, was unsuccessful. Raney nickel T-4, prepared according to Nishimura,[15] however, was found to be effective, as shown by the disappearance of the nitro group. The reduced material, after acid hydrolysis of the isopropylidene group and peracetylation, was fractionated by chromatography. Six different hexaacetylinosadiamine fractions were obtained, apparently in pure state, as shown by sharpness of the melting points. Configurational assignments were based on nmr spectroscopy, by which the numbers of axial and equatorial acetoxy and acetamido groups could be determined[8,12-14] as shown in Table I. These results were then compared with the predicted preferred conformation of each of the products that could have arisen from the sequence of reactions employed. Because three new asymmetric centers are created in the condensation of a dialdehyde with nitromethane, eight inosadiamines could be formed. The configurations

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CHART II

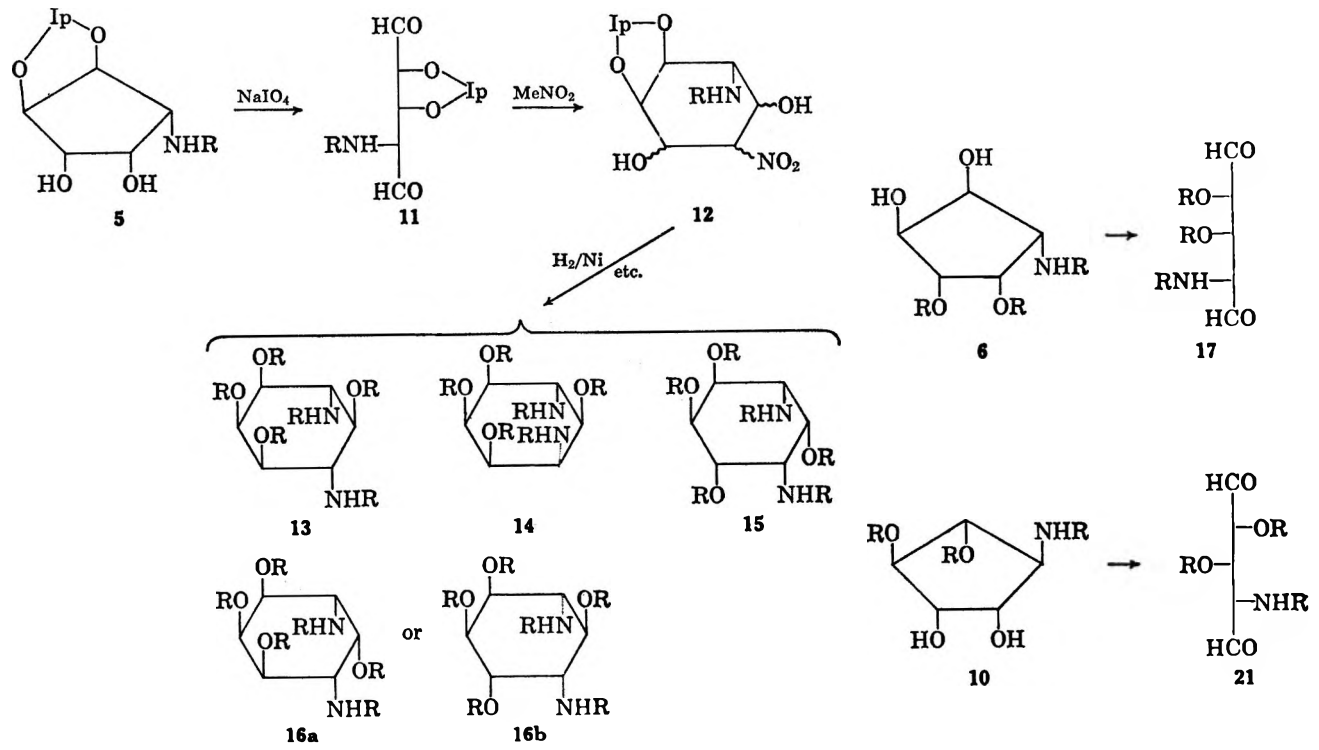


TABLE I

CHEMICAL SHIFTS OF ACETYL METHYL GROUPS OF INOSADIAMINES[a]

Compd	Trivial designation	Preferred conformation	Acetoxyl protons		Acetamido protons	
			Axial	Equatorial	Axial	Equatorial
13	*myo*-4,6	eaeeee	2.18 (3)	1.99 (9)		1.87 (6)
14	*epi*-2,6	eaeaee	2.20 (3)	2.00 (3), 1.93 (3), 1.89 (3)	2.00 (3)	1.87 (3)
15	*allo*-1,3	aeaeea	2.21 (3)	2.01 (3), 1.98 (6)	2.01 (6)	
16a or	*neo*-1,3	eaeeae	2.22 (6)	2.01 (6)		1.92 (6)
16b	*chiro*-2,4	eaaeee				
19	*myo*-1,5	eaeeee	2.16 (3)	2.08 (3), 2.01 (3), 1.97 (3)		1.90 (6)
20a or	*epi*-1,5	eaeaee	2.10 (6)	1.97 (3), 1.88 (3)		1.85 (6)
20b	*epi*-1,3					
23	*scyllo*-1,3	eeeeee		2.00 (12)		1.87 (6)
24	*myo*-1,3	eaeeee	2.24 (3)	2.01 (6), 2.00 (3)		1.90 (6)
25	*chiro*-1,3	eaaeee	2.19 (3)	2.00 (3), 1.98 (3), 1.97 (3)	2.00 (3)	1.95 (3)

[a] Spectra were measured on solutions in $CDCl_3$–CD_3OD (2:1 or 1:1). Values are reported on the δ scale. Numbers in parentheses refer to number of protons.

TABLE II

PREFERRED CONFORMATIONS OF INOSADIAMINES

Configuration	Root name	Conformation
1,2,3,4,5,6/0	*cis*-	aeaeae or eaeaea
1,2,3,4,5/6	*epi*-	eaeaee
1,2,3,4/5,6	*allo*-	aeaeea or eaeaae
1,2,3,5/4,6	*myo*-	eaeeee
1,2,4,5/3,6	*muco*-	eeeaaa or aaaeee
1,2,3/4,5,6	*neo*-	eaeeae
1,2,4/3,5,6	*chiro*-	aeeeea
1,3,5/2,4,6	*scyllo*-	eeeeee

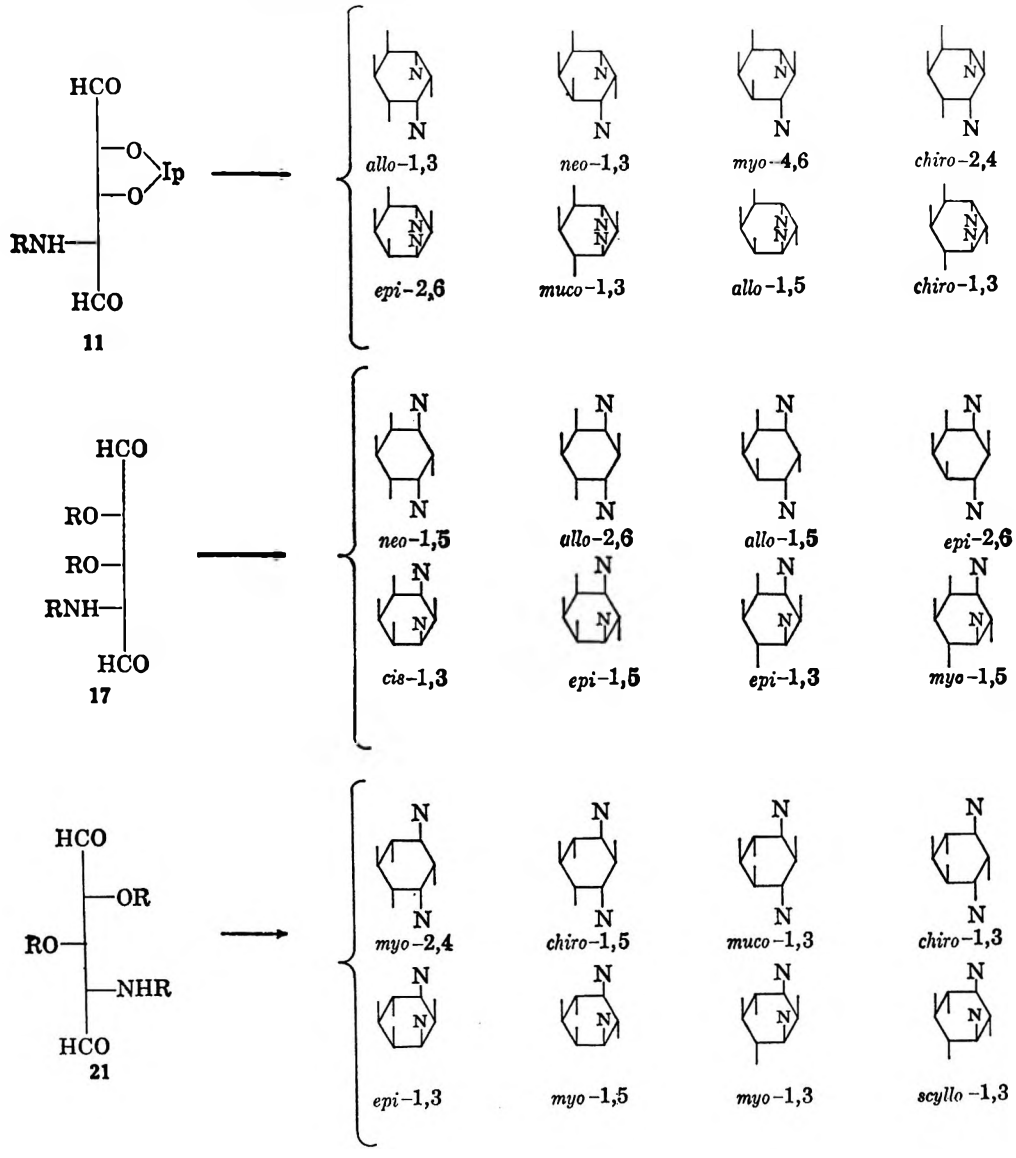
and conformations of these are indicated in Table II and Chart III. The total yield of pure products was 12%; so one cannot refer to "principal" or "minor" products of the cyclization reaction (see Experimental Section). The most abundant product isolated was considered to have configuration **13**, *i.e.*, *myo*-4,6, since it had one axial acetoxyl group, whereas the other three acetoxyl groups and both acetamido groups were equatorial. The two next most abundant products were assigned configurations **14** (DL-*epi*-2,6) and **15** (DL-*allo*-1,3). A fourth product, **16**, mp 296–299°, had two axial and two equatorial acetoxyl groups and two equatorial acetamido groups. This restricts the possible configuration to *neo*-1,3 (**16a**) and DL-*chiro*-2,4 (**16b**) but does not distinguish between these two possibilities. Two additional products of this reaction have not been identified.

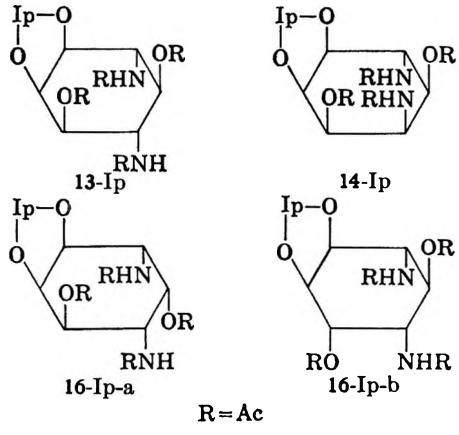
In a separate experiment the sequence of reactions was altered so that the mixture obtained after reduction of the nitro group was not acidified, but was acetylated directly to a mixture of monoisopropylidenetetraacetylinosadiamines. From this mixture four compounds were purified. Three of these correspond to the inosadiamines **13**, **14**, and **16**, since removal of the isopropylidene groups followed by peracetylation yielded compounds identical with the hexaacetyl derivatives previously prepared. The isopropylidene derivatives are designated as **13**-Ip, **14**-Ip, and **16**-Ip.

Inosadiamines from *ribo* Dialdehyde 17.—Three diastereoisomeric inosadiamines were obtained from the

CHART III

POSSIBLE CONFIGURATIONS AND TRIVIAL NAMES OF INOSADIAMINES THAT COULD BE DERIVED FROM THE THREE DIALDEHYDES USED IN THIS STUDY



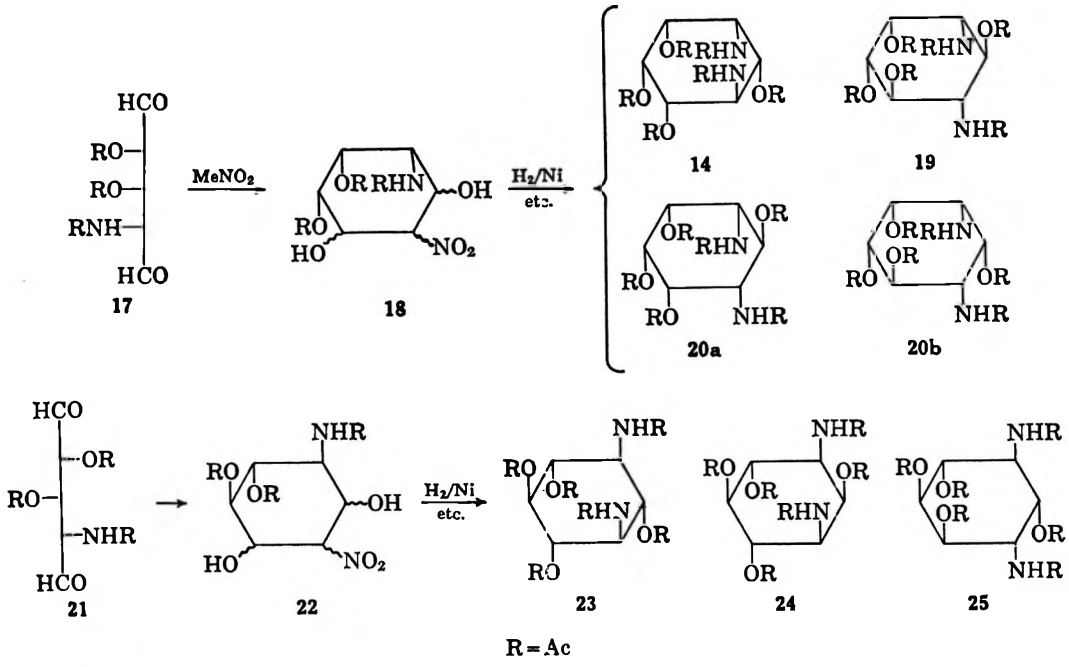


cyclization of the dialdehyde **17** (Chart IV). One of these is identical with the product designated as DL-*epi*-2,6 (**14**) which was obtained from dialdehyde **11**. Another product **19** had one axial acetoxyl group and all the other acetyl groups equatorial. Of the eight possible isomers (Chart III) only DL-*myo*-1,5 can assume such a conformation. The third product, **20**, had two each of axial and equatorial acetoxyl groups and two equatorial acetamido groups. Two of the possible compounds, *epi*-1,5 (**20a**) and DL-*epi*-1,3 (**20b**), could exist in this conformation. No further decision between these possibilities can be based on the available evidence.

Inosadiamines from *xylo* Dialdehyde 21.—Three products were obtained from the condensation of dialdehyde **21** with nitromethane (see Chart IV). In this case, all three of the compounds were previously known.[6-8] The physical and spectral properties of these substances agreed with those reported by the earlier workers. The compounds are the *scyllo*-1,3 (streptamine),[6] the *myo*-1,3,[7] and the DL-*chiro*-1,3[8] (structures **23**, **24**, and **25**, respectively; Chart IV).

Validity of use of Chemical Shift of Acetyl Groups for Configurational Assignments.—The correlations of chemical shift with the axial or equatorial orientation of acetoxyl and acetamido groups were established[8,12-14] on the basis of spectra measured on solutions in chloroform. Most of the new compounds reported here are insufficiently soluble in chloroform for the measurement of nmr spectra. The values reported in Table I are de-

CHART IV



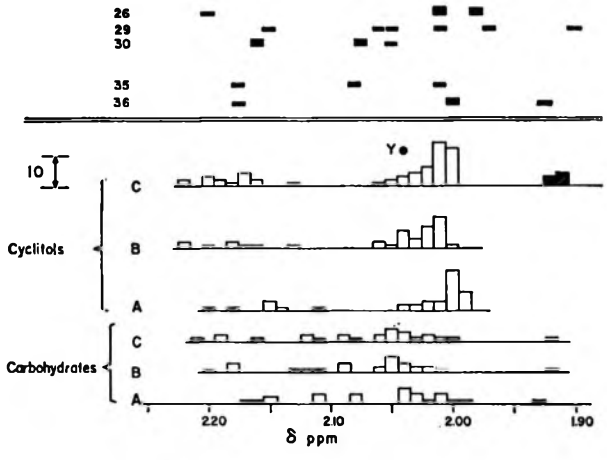


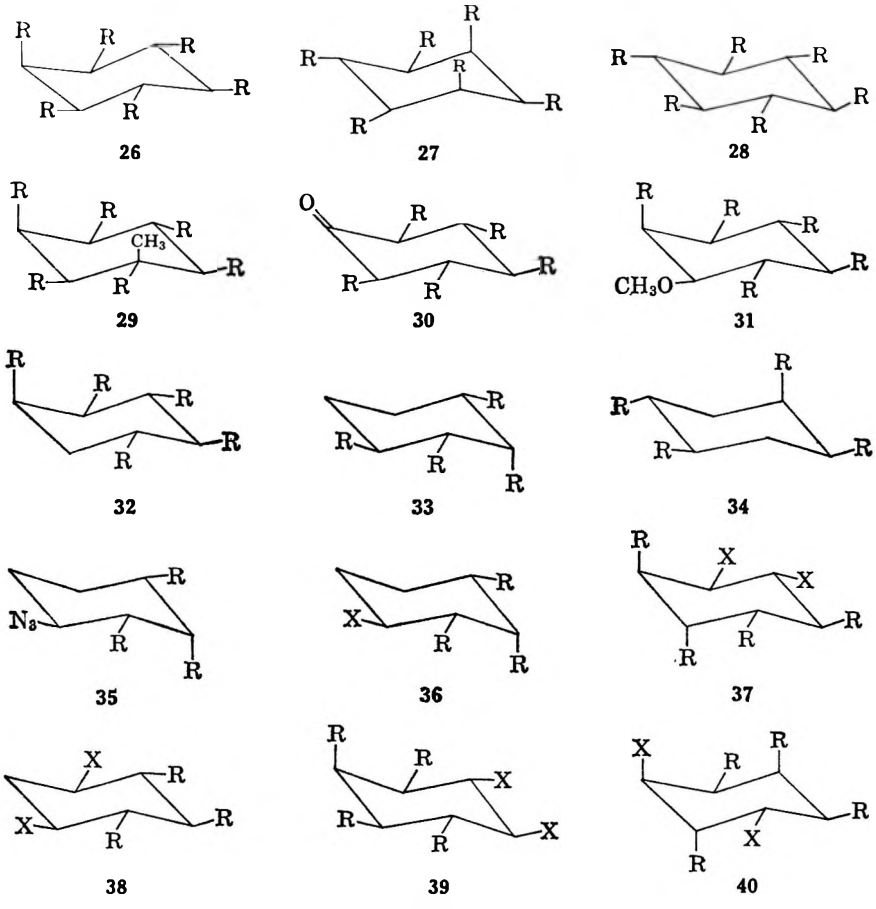
Figure 1.—Chemical shifts of acetyl protons of acetoxy and acetamido groups of carbohydrates and cyclitols. The diagonally hatched areas represent equatorial acetamido groups. Point Y represents an axial acetamido group in compound **40**. The remaining data refer to acetoxyl groups. The vertical axis in each case represents the number of signals observed at the indicated chemical shift, and the double arrow marked 10 shows the height equivalent to 10 signals in the histogram. A, B, and C indicate that the data are derived from spectra measured on solutions in $CDCl_3$, $CDCl_3$–CD_3OD (2:1), and $CDCl_3$–CD_3OD (1:1), respectively. The upper part of the figure shows the influence of magnetically anisotropic functional groups on chemical shifts of compounds with similar configurations. Not shown in the figure are the chemical shifts of the C–CH_3 group of laminitol (δ 1.56–1.58) and the O–CH_3 group of bornesitol (δ 3.36–3.38).

rived from spectra measured on solutions in a mixed solvent, either 2:1 or 1:1 (v/v) mixtures of $CDCl_3$ and CD_3OD. In view of the well-known influence of solvent composition on chemical shift, we considered a reexamination of the chemical shifts of acetyl groups in the mixed solvents essential. The results of such a study are shown in Figure 1. Five fully acetylated carbohydrates and fifteen fully acetylated cyclitols (including aminocyclitols) were studied. A definite solvent shift is observed when 2:1 or 1:1 $CDCl_3$–CD_3OD is substituted for pure $CDCl_3$. However, the shift is small and in no case does any ambiguity arise. The data for the carbohydrates and the cyclitols are reported separately in Figure 1 because the carbohydrate derivatives have two types of groups not found in the cyclitols, *viz.*, anomeric and primary acetoxyl groups. The axial anomeric acetoxyl signals are those at lowest field,[16,17] and the signals of equatorial anomeric acetoxyl groups are the only ones that may overlap with the "axial" region and may thus cause confusion in the assignments. In the case of the cyclitols, Figure 1 shows that the generalizations previously established[8,12–14] are still valid when the mixed solvent is used in place of pure $CDCl_3$.

The data for laminitol **29** and 2,4,6/3,5-pentahydroxycyclohexanone (*scyllo-ms*-inosose) **30** (Chart V) are given separately because both contain magnetically anisotropic groups. *Scyllo-ms*-inosose contains no axial acetoxyl groups but two of the groups give nmr signals at δ 2.16, *i.e.*, in the middle of the "axial" spectral region. This is due to a strong deshielding effect exerted by the ring carbonyl group, and these low-field signals probably represent the acetoxyl groups adjacent to the ring carbonyl. In the case of laminitol, the C-methyl group shields some and deshields other acetoxyl groups relative to the equatorial acetoxyl groups of *myo*-inositol. Even so, in spite of the presence of the anisotropic group the assignments seem unambiguous. On the basis of the results of Lichtenthaler and Emig[13d] the signal at δ 1.89 is assigned to the C(CH_3)–acetoxyl group. The anisotropic effect of the azido group is seen when the data for the azidotriol triacetate **35** are compared with those for the acetamidotriol triacetate **36**. One of the equatorial acetoxyl groups of **35** is deshielded by 0.08 ppm relative to **36**, whereas the other equatorial group and the axial group are unaffected. Similar observations on the effects of anisotropic groups have been published recently by Horton, *et al.*,[17] and by Cushley,

(16) D. Horton, J. B. Hughes, J. S. Jewell, K. D. Philips, and W. N. Turner, *J. Org. Chem.*, **32**, 1073 (1967).
(17) D. Horton, W. E. Mast, and K. D. Philips, *ibid.*, **32**, 1471 (1967).

CHART V
CYCLITOLS OF KNOWN CONFIGURATION USED IN STUDY OF CHEMICAL SHIFTS OF ACETYL GROUPS



R = OAc; X = NHAc

et al.[18] Since the new aminocyclitols listed in Table I contain the same type and number of substituents, the assignment of configuration based on chemical shifts appears to be safe.

^{14}C-Labeled Inosadiamines.—When the nature of the products was established, each of the condensation reactions was repeated as described, except that the nitromethane was labeled with ^{14}C. The usual procedures then gave a series of specifically labeled inosadiamines. A similar type of reaction was used by Drummond, *et al.*,[19] to prepare specifically labeled inosamines, which were then deaminated to give labeled inositols.

Discussion

The hexaacetyl derivative of the *allo*-1,3-diamine **15** can exist in two chair conformations in which nonbonded repulsions might be assumed to be nearly equivalent. The data in Table I suggest, however, that one of the conformers predominates, specifically the one in which the acetamido groups are axial. Two possible explanations of this finding are (a) that the combination of two axial acetamido groups and one axial acetoxyl group is sterically less demanding than are three axial acetoxyl groups and (b) that, when the acetamido groups are axial, one or both amide hydrogen atoms can more easily form hydrogen bonds. This hydrogen bonding would then make the "acetamide axial" conformer more stable. Study of Dreiding models shows that each amide hydrogen atom can approach within H-bonding distance of several potential electron-pair donors, including the carbonyl oxygen and the nitrogen atom of the other acetamido group, as well as the carbonyl oxygen atoms of adjacent equatorial acetoxyl groups. A situation which would be formally analogous to a dimeric form of acetic acid or acetamide, *i.e.*, that in which both amide hydrogens would be bonded simultaneously to the opposite carbonyl oxygens, appears to be excluded because of interference between the acetyl methyl groups. Further experimental work will be required to establish whether such hydrogen bonds are indeed present, and, if so, what acceptor atoms participate in the bonding. Similar arguments involving H bonding of the acetamide hydrogen atom can be used to justify the assignment of a favored conformation for the *muco*-inosadiamine **40** as shown in Chart V. The three *myo*-inosadiamines reported in Table I could also exist in chair conformations with *syn*-diaxial acetamido groups, but these conformations would have five substituents axial and only one equatorial, a most unfavorable situation. In a related study, Lichtenthaler and Leinert[13c] find that in the case of hexaacetyl-*cis*-inosatriamine-(1,3,5) the "acetamide equatorial" conformation is favored, rather than the axial conformations proposed in the present work. The conformation of the triamino compound is deduced from the nmr spec-

(18) R. J. Cushley, K. A. Watanabe, and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 394 (1967).

(19) G. I. Drummond, J. N. Aronson, and L. Anderson, *J. Org. Chem.*, **26**, 1601 (1961).

trum of a sample dissolved in D_2O, whereas in the present study spectroscopy was carried out on solutions in $CDCl_3$–CD_3OD whose polarity is much lower. Undoubtedly, the aqueous environment would have a greater tendency to disrupt intramolecular H bonds, so that this stabilizing factor would be absent. Furthermore, because of the greater polarity of acetamide groups relative to acetoxyl groups, one may postulate the existence of a solvent cage of D_2O molecules associated with the acetamido groups. Such a solvent cage would make these groups much larger than the acetoxyl groups, and thus would favor the "acetamide equatorial" conformation.

The chemical shifts observed in the case of the *epi*-2,6 isomer **14** are not easy to interpret, since the signals are at higher field than those of all the other compounds. By elimination of other possibilities we have arrived at the conclusion presented, but some reservations may be necessary, and the configurational assignment in this case, although reasonable, is only tentative.

The cyclopentane cyclitols and aminocyclitols[10,11] are convenient starting materials for the preparation of cyclohexane aminocyclitols. The disadvantage of these compounds is that so far none of the racemates has been resolved. However, methods exist for resolution of amino compounds, and this disadvantage can be overcome. The total synthesis of inosadiamines from cyclopentadiene represents the conversion of a petroleum by-product into compounds related to antibiotics, which are of potential interest in biological and medicinal chemistry. The same approach has been used for preparing deoxyinosadiamines,[20] and should be a useful step in the synthesis of labeled or modified antibiotics.

Experimental Section[21]

DL-1,2-O-Isopropylidene-(1,2/5)-5-acetamido-3-cyclopentene-1,2-diol (3).—A 10.4-g (43.2 mmol) sample of DL-1,2-di-O-acetyl-(1,2/5)-5-acetamido-3-cyclopentene-1,2-diol[11] (**1**) was dissolved in 100 ml of methanol saturated with dry NH_3 and 50 ml of absolute ethanol and left overnight at room temperature. The solvent and acetamide were evaporated under reduced pressure to give the syrupy acetamidodiol **2**. The latter was stirred 3 days with anhydrous acetone (450 ml), anhydrous $CuSO_4$ (50 g), and 0.5 ml 98% H_2SO_4. The green reaction mixture was neutralized with saturated methanolic NH_3 and filtered. Evaporation of solvent gave a syrup which crystallized from ether. Recrystallization from ether gave 6.74 g (79%) of plates (**3**), mp 98°. *Anal.* Calcd for $C_{10}H_{15}O_3N$ (197.24): C, 60.89; H, 7.67; N, 7.10. Found: C, 60.60; H, 7.52; N, 6.89.

DL-1,2-Di-O-acetyl-3,4-O-isopropylidene-(1,2,5/3,4)-5-acetamidocyclopentane-1,2,3,4-tetrol (4a).—To a solution of 2.8 g (14.2 mmol) of **3** in 400 ml of 95% ethanol, 10.5 g of $MgSO_4 \cdot 7H_2O$ was added; then 400 ml of 2% aqueous $KMnO_4$ was added, with stirring, over a period of 2 hr at −20°. The mixture was then left overnight at room temperature, filtered, treated with active carbon, and filtered again. Concentration in a rotary evaporator gave an amorphous substance, which was extracted with 100 ml of hot absolute ethanol. The ethanolic solution was evaporated to a yellow syrup; this was acetylated (10 ml of pyridine, 10 ml of acetic anhydride) overnight at room temperature. Removal of the reagents by evaporation gave a syrup which was chromatographed over Al_2O_3 (60 g, 1.8-cm diameter) with chloroform to give 2.93 g of crude **4a**. Recrystallization from ether gave 2.41 g (54%) of colorless needles, mp 108°. *Anal.* Calcd for $C_{14}H_{21}O_7N$ (315.32): C, 53.32; H, 6.71; N, 4.44. Found: C, 53.46; H, 6.58; N, 4.45.

DL-3,4-O-Isopropylidene-(1,2/3,4,5)-5-acetamidocyclopentane-1,2,3,4-tetrol (5).—Compound **4a** (1.267 g, 4.02 mmol) was dissolved in 50 ml of methanol saturated with NH_3 and 10 ml of methanol and left overnight at room temperature. Solvent and acetamide were evaporated. The crystalline residue was recrystallized from absolute ethanol–ether to give **5**, 675 mg (73%), as needles, mp 144–145°. *Anal.* Calcd for $C_{10}H_{17}O_5N$ (231.25): C, 51.94; H, 7.41; N, 6.06. Found: C, 51.84; H, 7.60; N, 6.12.

DL-1,2-Di-O-acetyl-(1,2,5/3,4)-5-acetamidocyclopentane-1,2,3,4-tetrol (6).—Compound **4a** (860 mg, 3.12 mmol) was dissolved in 60 ml of 50% acetic acid and heated for 1 hr at 100°. Removal of solvent gave a crystalline substance which was recrystallized from absolute ethanol–ether to yield 508 mg (68%) of **6** as colorless needles, mp 133°. *Anal.* Calcd for $C_{11}H_{17}O_7N$ (275.27): C, 47.99; H, 6.23; N, 5.09. Found: C, 47.48; H, 6.26; N, 5.18.

DL-1,2,3,4-Tetra-O-acetyl-(1,2,5/3,4)-5-acetamidocyclopentane-1,2,3,4-tetrol (7).—Compound **6** (40 mg, 0.14 mmol) was acetylated (2.0 ml of pyridine, 1.0 ml of acetic anhydride, 2 days at room temperature) and worked up as usual. Ether (2 ml) was added to the syrupy residue, and after standing at −10° for several days the product crystallized. Recrystallization from ether gave plates (48 mg, 89%), mp 119°. A mixture melting point with authentic[11] **7** was not depressed, and the infrared spectra were identical.

DL-3,4-Di-O-acetyl-1,2-O-isopropylidene-(1,2,4/3,5)-5-acetamidocyclopentane-1,2,3,4-tetrol (9).—To a solution of 2.5 g (10.4 mmol) of DL-1,2-di-O-acetyl-(1/2,5)-5-acetamido-3-cyclopentene-1,2-diol[11] (**8**) in 250 ml of 95% ethanol, 7.5 g of $MgSO_4 \cdot 7H_2O$ was added. The solution was stirred and maintained at −20° for 1 hr while 272 ml of 1% aqueous $KMnO_4$ was added. After standing overnight at room temperature the mixture was filtered; the filtrate was treated with active carbon, refiltered, and then concentrated. The amorphous residue was extracted with 100 ml of hot absolute ethanol, and the syrupy product obtained after evaporation of the ethanol was treated with 450 ml of anhydrous acetone, 10 g of anhydrous $CuSO_4$, and 0.2 ml of 98% H_2SO_4, and stirred for 2 days. The product was worked up as usual, and the syrup obtained was chromatographed over Al_2O_3 (80 g, 1.8-cm diameter) with chloroform to give crude **9** (1.46 g, 44%). Crystallization from ether gave needles, mp 147–150°. *Anal.* Calcd for $C_{14}H_{21}O_7N$ (315.31): C, 53.32; H, 6.71; N, 4.44. Found: C, 53.10; H, 6.58; N, 4.35.

DL-3,4-Di-O-acetyl-(1,2,4/3,5)-5-acetamidocyclopentane-1,2,3,4-tetrol (10).—The isopropylidene derivative **9** (150 mg, 0.48 mmol) was dissolved in 10 ml of 50% acetic acid and heated for 2 hr at 100°. After removal of solvents a slightly yellow syrup (**10**) was obtained. Attempts to crystallize this product were unsuccessful.

4,6-Diacetamido-1,2,3,5-tetra-O-acetyl-4,6-dideoxy-*myo*-inositol (13), DL-2,6-Diacetamido-1,3,4,5-tetra-O-acetyl-2,6-dideoxy-*epi*-inositol (14), DL-1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*allo*-inositol (15), and 1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*neo*-inositol (16a) or DL-2,4-Diacetamido-1,3,5,6-tetra-O-acetyl-2,4-dideoxy-*chiro*-inositol (16b).—The acetamido isopropylidene compound **5** (630 mg, 2.72 mmol) was dissolved in 15 ml of water containing 600 mg of $NaIO_4$ and the solution was left overnight at room temperature. After evaporation of water, the residue was extracted with 50 ml of hot ethanol–chloroform (1:1). When this solvent was evaporated a yellowish syrup (*lyxo*-dialdehyde **11**) was obtained, which was used without further purification for the next reaction. The syrup was dissolved in 10 ml of absolute ethanol, and 750 mg of nitromethane was added. The solution was cooled and maintained between 0 and −5° while 7 ml of "2% sodium alcoholate" (2 g of Na in 100 ml of ethanol) was added dropwise over a period of 10 min with stirring; the stirring was continued for 2 hr. The mixture was then left overnight at 5°. Yellow crystals separated; these were dissolved in 100 ml of methanol and the solution was treated with Amberlite IRC-50-H^+ to remove sodium ions. The solvent was evaporated, leaving a yellow syrup **12** whose infrared spectrum showed absorption at frequencies characteristic of the following functional groups: OH (3400 cm^{-1}), NO_2 (1541 cm^{-1}),

(20) A. Hasegawa and H. Z. Sable, unpublished data.

(21) Melting points were determined on a Kofler Micro hot stage (A. H. Thomas and Co.) and are corrected. Boiling points are uncorrected. Nmr spectra were recorded with a Varian Associates A-60 nmr spectrometer. Infrared spectra were recorded with a Perkin-Elmer Model 237B spectrophotometer. Radioactivity was measured on thin samples on steel planchets, with a Nuclear-Chicago Corp. Model 183B counter. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Proportions indicated for mixed solvents refer to volume per volume ratios. For chromatography, Merck aluminum oxide, acid washed, was used.

acetamido carbonyl (1640 cm^{-1}), and isopropylidenedioxy (842 cm^{-1}). The crude nitro compound **12** was dissolved in 50 ml of 50% aqueous ethanol; 3.0 g of Raney nickel T-4 catalyst[15] was added and hydrogen as bubbled through for 2 hr while the solution was stirred and maintained at 60–65°. The solution was then made slightly acidic by addition of 2 *N* HCl and then hydrogen was passed in for 5 hr. After removal of the catalyst by filtration the solution was acidified with 5 ml of concentrated HCl, the solvents were removed, and the residual syrup was acetylated. The acetylated product was chromatographed over Al_2O_3 (50 g, 1.0-cm diameter) with chloroform and chloroform–ethanol (1:1). The crystalline products obtained from the eluates were recrystallized from absolute ethanol or ethanol–ether (1:1). The first eluate fraction (20 ml of chloroform) yielded 3.5 mg (0.3%) of unidentified needles, mp 250°. A second fraction (50 ml of chloroform) gave 20.5 mg (1.8%) of unidentified prisms (correct analysis for an inosadiamine hexaacetate); these were transformed into needles at 262–263° and melted with sublimation at 300–310°. A third elution (20 ml of chloroform–ethanol) gave 604 mg of syrup which was crystallized from ethanol–ether. Fractional recrystallization of this product from ethanol gave 23 mg (2%) of needles, mp 318–320° dec, identified as **15**, and 48 mg (4.1%) of prisms, mp 250–255° dec, identified as **13**. The combined mother liquors of this fraction were evaporated to a syrup which was dissolved in 10 ml of ethanol–ether and left at 5° for 2 weeks. The crystalline material was fractionally recrystallized from ethanol to give 43 mg (3.7%) of needles, mp 280–283° dec, identified as **14**, and 15 mg (1.3%) of needles, mp 296–299°, identified as **16**. Elemental analysis of **16** was not carried out. *Anal.* Calcd for $C_{18}H_{26}O_{10}N_2$ (430.4): C, 50.19; H, 6.09; N, 6.51. Found for **13**: C, 50.31; H, 6.21; N, 6.59. Found for **14**: C, 50.10; H, 6.17; N, 6.60. Found for **15**: C, 50.39; H, 6.52; N, 6.70. Found for the unidentified prisms: C, 50.28; H, 6.35; N, 6.70.

^{14}C-Labeled Inosadiamines 13, 14, and 15.—The sequence of reactions described in the previous section was repeated, radioactive nitromethane[22] being used. The amounts of starting material were 580 mg of acetamidoisopropylidenetetrol **5** and 750 mg of ^{14}C-nitromethane. The amounts and measured radioactivity of the products were **13**, 45 mg, 3830 cpm/mg; **14**, 33 mg, 4000 cpm/mg; and **15**, 18 mg, 3970 cpm/mg.

DL-4,6-Diacetamido-1,5-di-O-acetyl-4,6-dideoxy-2,3-O-isopropylidene-*myo*-inositol (13-Ip), DL-2,6-Diacetamido-1,3-di-O-acetyl-2,6-dideoxy-4,5-O-isopropylidene-*epi*-inositol (14-Ip), and DL-1,3-Diacetamido-2,4-di-O-acetyl-1,3-dideoxy-5,6-O-isopropylidene-*neo*-inositol (16-Ip-a) or DL-2,4-Diacetamido-1,3-di-O-acetyl-2,4-dideoxy-5,6-O-isopropylidene-*chiro*-inositol (16-Ip-b).—The sequence of reactions used in the previous two sections was repeated with the modifications noted. Crude *lyxo* dialdehyde **11** derived from 580 mg of **5** was dissolved in 15 ml of ethanol and treated with 0.7 ml of nitromethane and 0.7 ml of 2% sodium methylate. The work-up was carried out as described, except that, after removal of the catalyst by filtration, concentrated HCl was not added. Instead the neutral solution was evaporated to a syrup which was acetylated as usual (10 ml of pyridine and 5 ml of acetic anhydride) and the crude product was chromatographed over Al_2O_3 (40 g, 1.8-cm diameter). In each case, removal of the solvent gave a syrup which was crystallized by addition of ether–ethanol (3:1) and recrystallized from ethanol. The first portion of eluate (60 ml of chloroform) gave 35.1 mg of **14-Ip** as needles, mp 246–248°, and 16 mg of an unidentified substance as needles, mp 235–236°. The second eluate (20 ml of chloroform–ethanol, 1:1) gave a residue which was fractionally crystallized from ethanol to give 35.6 mg of **13-Ip** as needles, mp 294–296° dec, and 48.2 mg of **16-Ip** as needles, mp 283–285°. Each of the substances identified had infrared spectra consistent with the functional groups present and the nmr spectra were correct for compounds with two acetoxyl, two acetamido, and two O-isopropylidene methyl groups. Identification was achieved as follows. The isopropylidene derivative (15 mg) was dissolved in 3 ml of 2 *N* HCl and heated at 50° for 30 min, the solvent was evaporated, and the residue was acetylated as usual. The products were crystallized from ethanol–ether and recrystallized from ethanol, to give 10–11 mg of substances whose melting points and infrared and nmr spectra were identical with those of the authentic hexaacetyl compounds **13**, **14**, and **16**.

DL-2,6-Diacetamido-1,3,4,5-tetra-O-acetyl-2,6-dideoxy-*epi*-inositol (14), DL-1,5-Diacetamido-2,3,4,6-tetra-O-acetyl-1,5-dideoxy-*myo*-inositol (19), and 1,5-Diacetamido-2,3,4,6-tetra-O-acetyl-1,5-dideoxy-*epi*-inositol (20a) or DL-1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*epi*-inositol (20b).—The *ribo* dialdehyde **17** was prepared from glycol **6** (654 mg, 2.37 mmol) by treatment with $NaIO_4$ (510 mg in 20 ml of water), extraction with hot ethanol, and evaporation to a syrup as described above. The syrupy product was dissolved in 15 ml of absolute ethanol, 600 mg of nitromethane was added, and the solution was maintained between 0 and −5° while 7 ml of 2% sodium ethylate was added (10 min); stirring was continued for 2 hr and the mixture was stored overnight at 5°. The product consisted of a precipitate **18a** and a soluble portion **18b**. These were separated by filtration and were worked up separately as described above, to give hexaacetyl inosadiamines. The product derived from **18a** was chromatographed on Al_2O_3 (50 g, 1.0-cm diameter) with chloroform–ethanol (1:1), and the crystalline product was fractionally recrystallized from ethanol to give 68.5 mg (6.7%) of needles, mp 295–300° dec, identified as **20**, and 11 mg (1.1%) of needles, mp 280–283°, identical with **14** described above. Chromatography of the product from **18b** on Al_2O_3 (20 g, 0.8-cm diameter) with chloroform (20 ml) gave 144 mg of a syrupy substance which was crystallized by addition of 3 ml of ether and 5 ml of ethanol. Fractional recrystallization from ethanol gave 44.2 mg (4.3%) of needles, mp 297–298°, identified as **19**, and an additional 8 mg (0.8%) of **14**. *Anal.* Calcd for $C_{18}H_{26}O_{10}N_2$ (430.4): C, 50.19; H, 6.09; N, 6.51. Found for **19**: C, 50.25; H, 6.31; N, 6.55. Found for **20**: C, 50.31; H, 6.28; N, 6.51.

^{14}C-Labeled Inosadiamines 19 and 20.—The sequence of reactions described in the previous section was repeated, radioactive nitromethane[22] being used. The amounts of starting material used were 486 mg of glycol **6** and 530 mg of nitromethane (12.7 μCi). The amounts and measured radioactivity of the products were **19**, 30 mg, 3900 cpm/mg and **20**, 43 mg, 4600 cpm/mg.

1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*scyllo*-inositol (23), 1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*myo*-inositol (24), and DL-1,3-Diacetamido-2,4,5,6-tetra-O-acetyl-1,3-dideoxy-*chiro*-inositol (25).—The *xylo* dialdehyde **21** was prepared from the acetamidocyclopentanetetrol derivative **10** (315 mg, 1.14 mmol in 7 ml of water) by treatment with $NaIO_4$ (220 mg) in the usual manner. After removal of water the residue was extracted with 30 ml of hot chloroform, the solvent was evaporated and the syrupy dialdehyde **21** was dissolved in 8 ml of absolute ethanol. This solution was treated with nitromethane (320 mg) and 2% sodium ethylate as described above, except that stirring was continued for 5 hr before storage at 5° overnight. The yellow crystals which formed were collected, dissolved in methanol (50 ml), and worked up as before. The mixture of acetylated inosadiamines was chromatographed on Al_2O_3 (20 g, 0.8-cm diameter). The first eluate (chloroform, 30 ml) yielded 75 mg of syrup which crystallized from ethanol–ether. Recrystallization from ethanol gave 30 mg (6.2%) of **25**, mp 219°. The second eluate (chloroform–ethanol 1:1, 50 ml) gave 90 mg of crystals which were fractionally recrystallized from ethanol to give 15 mg (3.1%) of needles, mp 245–250°, identified as **23**, and 65 mg (13.2%) of needles, mp 270–271°, identified as **24**. The infrared spectra of these compounds were identical with those of authentic samples.[6–8]

^{14}C-Labeled Inosadiamines 23 and 24.—The sequence of reactions just described was repeated, radioactive nitromethane[22] being used. The amounts of starting materials were 250 mg of glycol **10**, 500 mg of nitromethane (12 μCi), and 2.3 ml of sodium ethylate. The amounts and radioactivity of the products were **23**, 9 mg, 4370 cpm/mg and **24**, 48 mg, 4860 cpm/mg.

Acetylation of Cyclitols.—Cyclitols (tetrols and inositols) were acetylated as follows. Cyclitol (60–80 mg) was dissolved in 0.3–0.4 ml of dry pyridine, 0.2–0.3 ml of acetic anhydride was added, and the mixture was left at room temperature for 2 days. The reagents were removed at reduced pressure, a few milliliters of water were added and the mixture was reevaporated. The products were recrystallized from ethanol.

Source of Compounds Used in the Nmr Study. A. Carbohydrates.—The five carbohydrate derivatives used were purchased from commercial sources as follows: α-D-glucopyranose pentaacetate, mp 114–115°, from Eastman Kodak Chemicals; β-D-glucopyranose pentaacetate, mp 133–134°, and β-D-glucos-

(22) ^{14}C-Labeled nitromethane with an indicated specific activity of 240 μCi/g was obtained from Volk Radiochemical Co., Skokie, Ill. In the experiments described this material was diluted to one-tenth the specific activity by addition of nine parts of nonradioactive nitromethane. This diluted material was assumed to have a specific activity of 24 μCi/g. The radioactivity of the products is reported in cpm (counts per minute above background) and not converted into the Curie scale.

amine pentaacetate, mp 182.5–183.5°, from Sigma Chemical Co.; α-D-galactopyranose pentaacetate, mp 94–98°, and β-D-galactopyranose pentaacetate, mp 144–147°, from Aldrich Chemical Co.

B. Cyclitols.[23]—*myo*-Inositol hexaacetate **26**, mp 217–218° (lit.[24] 216°), was prepared by acetylation of *myo*-inositol (General Biochemicals, Inc., Chagrin Falls, Ohio). *epi*-Inositol hexaacetate **27**, mp 183–184° (lit.[25] 188°), was prepared by acetylation of *epi*-inositol kindly supplied by Professor T. Posternak. Hexa-O-acetyl-*scyllo*-inositol (**28**), hexa-O-acetyllaminitol (**29**), penta-O-acetyl-*scyllo*-*ms*-inosose (**30**), penta-O-acetyl bornesitol (**31**), and penta-O-acetyl viburnitol (**32**) were gifts from Professor T. Posternak. Tetraacetates of DL-(1,2,3/4)-tetrol[26a] (**33**), mp 112.5–113.5°, and DL(1,2,4/5)-tetrol[26b] (**34**), mp 91.5–92.5° (lit.[27] 93°), were prepared by acetylation of the corresponding tetrols.[26-28] The azidotriol triacetate[26a] **35**, mp 84–85.5°, was prepared from the corresponding azidotriol, and the acetamidotriol triacetate **36**, mp 157–159°, was prepared by catalytic hydrogenation of the corresponding cyclohexene compound, "conduramine C-4," previously reported by one of us.[29] Inosodiamines **37**, **38**, **39**, and **40** were described previously.[8,29]

Registry No.—**3**, 16019-90-2; **4a**, 16019-91-3; **5**, 16019-92-4; **6**, 16019-93-5; **9**, 16019-91-3; **12**, 16019-95-7; **13**, 6730-22-9; **13**-Ip, 16019-97-9; C-labeled **13**, 16019-98-0; **14**, 16020-12-5; **14**-Ip, 16020-13-6; C-labeled **14**, 16019-99-1; **15**, 16020-00-1; C-labeled **15**, 16020-01-2; **16a**, 16020-02-3; **16b**, 16020-03-4; **16a**-Ip, 16020-04-5; **16b**-Ip, 16020-05-6; **19**, 16020-06-7; **20a**, 16020-07-8; **20b**, 16020-08-9; **23**, 7380-63-4; **24**, 6255-71-6; **25**, 16020-11-4.

Acknowledgments.—The authors are grateful to Professor T. Posternak of the University of Geneva for gifts of several rare compounds used in the nmr studies.

(23) Trivial names are given for most of these compounds.

(24) E. G. Griffin and J. M. Nelson, *J. Amer. Chem. Soc.*, **37**, 1556 (1915).

(25) T. Posternak, *Helv. Chim. Acta*, **19**, 1333 (1936).

(26) Preparation and structure proof of these compounds will be described in subsequent papers in this series: (a) H. Z. Sable, H. Katchian, C. B. Niewoehner, and S. B. Kadlec, manuscript in preparation. (b) H. Z. Sable and A. L. Simonesen, manuscript in preparation.

(27) G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **28**, 894 (1963).

(28) N. D. Zelinski, Y. I. Denisenko, and M. S. Eventova, *Dokl. Akad. Nauk. USSR*, **1**, 313 (1935).

(29) (a) M. Nakajima, A. Hasegawa, and N. Kurihara, *Chem. Ber.*, **95**, 2708 (1962); (b) *Tetrahedron Lett.* 967 (1964); (c) *Ann. Chem.*, **689**, 235 (1965).

Mass Spectrometry in Structural and Stereochemical Problems. CXLII.[1] Electron Impact Induced Analogies to Thermal Elimination Processes in S-Methyl Xanthates and Esters[2]

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The mass spectra of the epimeric 2-methylcyclohexyl-S-methyl xanthates, acetates, and higher esters have been examined. By a combination of deuterium-labeling techniques and high resolution mass spectrometry, the principal modes of fragmentation of members of these classes have been uncovered. Evidence has been found for the existence of an electron impact induced analog to the thermal Chugaev reaction and, although ring conformational mobility complicates the interpretation of the experimental data, some stereospecificity favoring *cis* elimination appears to exist. Ring conformational freedom obviates any sound stereochemical conclusions in the ester cases. The positional specificity of the analogous elimination processes in all 2-methylcyclohexyl-S-methyl xanthates and esters is found to be high (79–85% 1,2 elimination and independent of the energy of the ionizing electron beam). The corresponding pyrolytic processes have been studied in detail in the epimeric d_0- and 2-d_1-methylcyclohexyl-S-methyl xanthates and acetates and these results are contrasted with those from the electron impact studies. In terms of percentage of the total elimination process, values found for the portion of the electron impact induced elimination which proceeds toward the tertiary center (C-2) are found to be 47% in *cis*-2-methylcyclohexyl-S-methyl xanthate (**5**), 90% in *trans*-2-methylcyclohexyl-S-methyl xanthate (**6**), 42% in *cis*-2-methylcyclohexyl acetate (**7**), and 38% in *trans*-2-methylcyclohexyl acetate (**8**). The corresponding losses in the pyrolytic elimination mode are 29% in **5**, 65% in **6**, 9% in **7**, and 56% in **8**.

In the recent literature[3] have appeared numerous references to analogies existing between thermal and electron impact induced reactions of organic compounds.

It has been pointed out[4] that one of the most general mass spectrometric hydrogen-transfer processes,[5] the McLafferty rearrangement,[6] *i.e.*, electron impact induced β cleavage with concomitant transfer of a γ-hydrogen atom[7] (see a → b), may, in the case of certain esters (c → d),[8] be regarded as the mass spectrometric counterpart to the well-known ester

(1) For paper CXLI, see J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **32**, 3904 (1967).

(2) Financial assistance (Grants No. CA-07195 and AM-04257) from the National Institutes of Health of the U. S. Public Health Service is gratefully acknowledged. The purchase of the Atlas CH-4 mass spectrometer was made possible through NASA Grant NsG 81-60.

(3) (a) F. W. McLafferty and R. J. Gohlke, *Anal. Chem.*, **31**, 2076 (1959); (b) E. K. Field and S. Meyerson, *Chem. Commun.*, 474 (1965); (c) S. Meyerson, *Rec. Chem. Progr.* (Kresge-Hooker Sci. Lib.), **26**, 257 (1965); (d) F. Weiss, A. Isard, and G. Bonnard, *Bull. Soc. Chim. Fr.*, 2332 (1965); (e) J. H. Beynon, R. F. Curtis, and A. E. Williams, *Chem. Commun.*, 237 (1966); (f) R. F. C. Brown, W. D. Crow, and R. K. Solly, *Chem. Ind.* (London), 343 (1966); (g) R. F. C. Brown; D. V. Gardner, J. F. W. McOmie, and R. K. Solly, *Chem. Commun.*, 407 (1966); (h) R. F. C. Brown and R. K. Solly, *Aust. J. Chem.*, **19**, 1045 (1966); (i) M. P. Cava, M. J. Mitchell, D. C. DeJongh, and R. Y. Van Fossen, *Tetrahedron Lett.*, 2947 (1966); (j) J. L. Cotter and G. J. Knight, *Chem. Commun.*, 336 (1966); (k) E. K. Field and S. Meyerson, *J. Amer. Chem. Soc.*, **88**, 21 (1966); (l) *ibid.*, **88**, 2836 (1966); (m) *ibid.*, **88**, 3388 (1966); (n) E. K. Field and S. Meyerson, *J. Org. Chem.*, **31**, 3307 (1966); (o) S. Meyerson and E. K. Field, *Chem. Commun.*, 275 (1966); (p) J. G. Pritchard and P. T. Funke, *J. Heterocycl. Chem.*, **3**, 209 (1966); (q) D. C. DeJongh, R. Y. Van Fossen, and C. F. Bourgeois, *Tetrahedron Lett.*, 271 (1967); (r) J. I. Jones and H. M. Paisley, *Chem. Commun.*, 128 (1967); (s) D. F. Lindow and L. Friedman, *J. Amer. Chem. Soc.*, **89**, 1271 (1967).

(4) G. Spiteller and M. Spiteller-Friedmann, *Monatsh.*, **95**, 257 (1964).

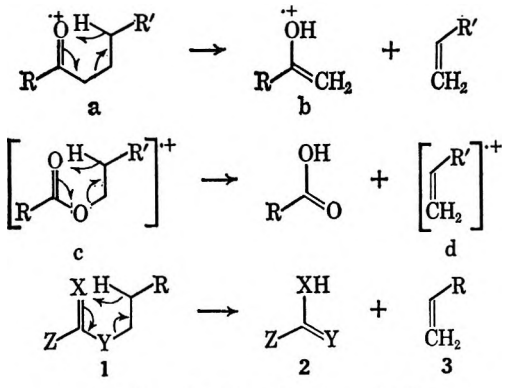
(5) *Cf.* C. Djerassi, *Pure Appl. Chem.*, **9**, 159 (1964).

(6) F. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).

(7) For a detailed review, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, Chapter 3.

(8) (a) W. Benz and K. Biemann, *J. Amer. Chem. Soc.*, **86**, 2375 (1964); (b) C. Djerassi and C. Fenselau, *ibid.*, **87**, 5756 (1965).

and Chugaev xanthate pyrolyses[9] (see 1 → 2 + 3). It should be noted that in ketones (a) the charge remains predominantly with the oxygen-containing moiety, while in esters (c) of higher alcohols, the olefin portion (d) retains most of the charge. In the thermally induced process the hydrogen abstraction is known to be *cis* cyclic in nature[9] and pyrolytic



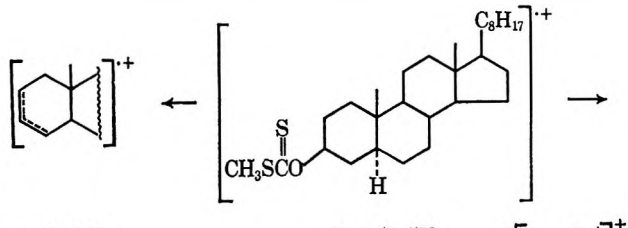
X = S; Y = O; Z = -SCH$_3$
or X = O; Y = O; Z = -CH$_3$

reactions have found wide synthetic utility as a result of their stereoselectivity. In esters, the acid fragment (2) produced is thermally stable, whereas that species produced in the xanthate case undergoes further decomposition to mercaptan (RSH) and carbonyl sulfide.

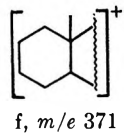
The over-all similarity in the behavior of esters with available β hydrogens in the electron impact (c → d) and pyrolytic (1 → 2 + 3) modes of breakdown prompted us to examine the stereochemical requirements of the radical-ion process, since nothing is known about it in contrast to the extensive body of knowledge existing for the thermal reaction.[9]

Results and Discussion

As some steroidal xanthates were at hand in the course of another study,[10] the mass spectra of these were examined for the presence of peaks corresponding to the ionized olefin, the expected fragment if a process corresponding to c → d were operating. The low-resolution mass spectrum (12 eV) of 5α-cholestan-3β-ol S-methyl xanthate (4) is representative and the higher mass portion of it is reproduced in Figure 1. In fact, it will be noted that the two most important peaks correspond to the ionized olefin (e) and the even-electron ion (f) formed by C(3)–O bond cleav-



e, *m/e* 370 4, *m/e* 478



f, *m/e* 371

(9) For leading references and an excellent review of such pyrolytic processes, see (a) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960); (b) H. R. Nace, *Org. Reactions*, **12**, 57 (1962).

(10) W. S. Briggs and C. Djerassi, *Tetrahedron*, **21**, 3455 (1965).

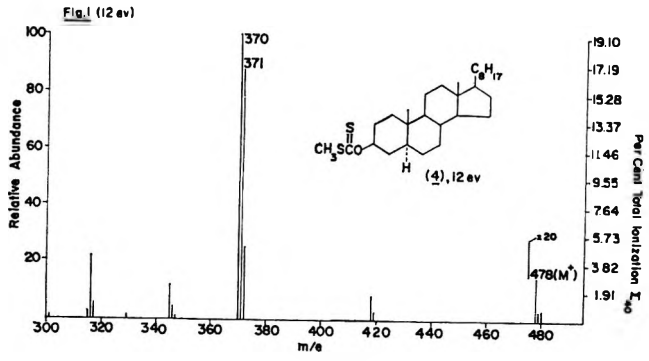
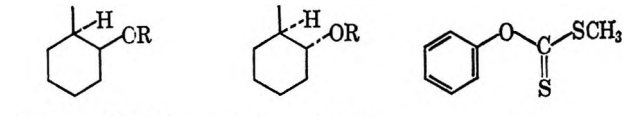


Figure 1.—Partial mass spectrum of 5α-cholestan-3β-ol S-methyl xanthate at 12 eV (A.E.I. MS-9 mass spectrometer).

age. Under the instrumental conditions employed for the measurements of the spectrum of this compound, it is conceivable that the peak at *m/e* 370 arose from ionization of olefin produced pyrolytically in the ion source of the mass spectrometer. However, the presence of a weak metastable ion at *m/e* 286.0 (calcd 286.1) corresponding to the process *m/e* 478 → *m/e* 370 established that at least a portion of the observed olefinic fragment e resulted by direct loss of the elements of xanthic acid from the molecular ion.

In the selection of a system in which to study the course and stereochemistry of the electron impact induced elimination reactions in esters and xanthates, primary consideration was given to the need for differentiation between *cis* and *trans* modes of elimination. Furthermore, sufficiently volatile S-methyl xanthates were required to allow introduction of the sample into the mass spectrometer at temperatures low enough to avoid complications in spectral interpretation arising by operation of competing thermal processes. The system chosen for this particular study was the 2-methylcyclohexyl moiety[11] in which the ring methyl may be disposed in either a *cis* or *trans* relationship to the ester or xanthate function. Compounds synthesized initially (see Experimental Section) were *cis*- (5) and *trans*-2-methylcyclohexyl-S-methyl xanthate (6) and the corresponding *cis* (7) and *trans* acetates (8).

At the outset it was hoped that the mass spectra of the two possible olefins formed by 1,2 elimination,



5, R = -CSCH$_3$ (S) 6, R = -CSCH$_3$ (S) 9

7, R = -CCH$_3$ (O) 8, R = -CCH$_3$ (O)

namely, 1-methyl-1-cyclohexene (Figure 2) and 3-methyl-1-cyclohexene, would differ significantly,[12]

(11) However, as will be pointed out later, this system suffers from the disadvantage of ring conformational mobility which complicates the interpretation of the results. See also (a) J. Cason and K.-L. Liauw, *J. Org. Chem.*, **30**, 1763 (1965); (b) J. Cason and A. I. A. Khodair, *ibid.*, **32**, 575 (1967).

(12) Consideration of the differences in the retro-Diels–Alder fragments of menth-1-ene and menth-2-ene has recently allowed conclusions to be drawn regarding the direction of electron impact induced acetic acid elimination in carvomenthyl acetate [see A. F. Thomas and B. Willhalm, *J. Chem. Soc., Sect. B*, 219 (1966)].

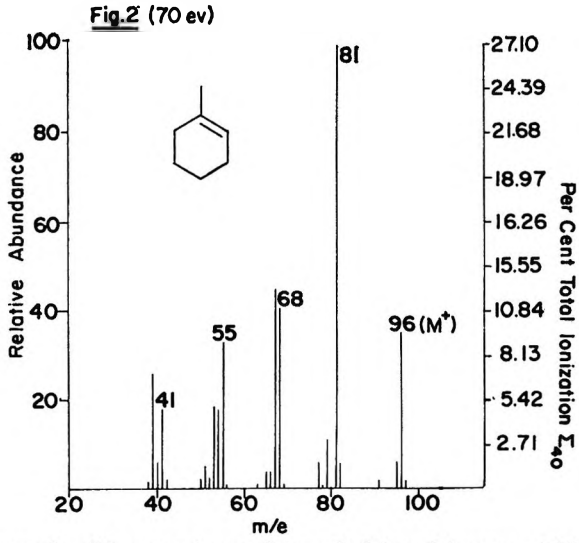


Figure 2.—Mass spectrum of 1-methyl-1-cyclohexene at 70 eV (Atlas CH-4 mass spectrometer).

thus allowing direct quantitative assessment of the preferred direction of elimination in **5**–**8**. However, the spectra of these two olefins were found to be virtually superimposable.[13] Thus, it was necessary to turn to deuterium-labeled substrates in order to determine unambiguously the course of these elimination processes. The syntheses of the required deuterated compounds are described later.

2-Methylcyclohexyl Xanthates.—The low resolution mass spectra of xanthates **5** and **6** determined at 70 and 14 eV by cold ion source techniques[14] are reproduced in Figures 3 and 4, and in Table I are reported

TABLE I

METASTABLE TRANSITIONS AND ELEMENTAL COMPOSITIONS OF FRAGMENTS FROM 2-METHYLCYCLOHEXYL-S-METHYL XANTHATES

Transition				Calcd	Found for *cis*-xanthate (**5**)	Found for *trans*-xanthate (**6**)
$C_9H_{16}OS_2^{\cdot+}$ [a]	→ $C_7H_{12}^{\cdot+}$	+ $C_2H_4OS_2$		45.1	45.2	45.2
(204^+	→ 96^+	+ 108)				
$C_7H_{13}^+$	→ $C_5H_9^+$	+ C_2H_4		49.1	49.1	49.1
(97^+	→ 69^+	+ 28)				
$C_7H_{13}^+$	→ $C_4H_7^+$	+ C_3H_6		31.2	31.2	31.2
(97^+	→ 55^+	+ 42)				
$C_7H_{12}^{\cdot+}$	→ $C_6H_9^+$	+ $CH_3\cdot$		68.4	68.4[b]	68.4[b]
(96^+	→ 81^+	+ 15)				
$C_6H_9^+$	→ $C_4H_7^+$	+ C_2H_2		37.3	37.2	37.2
(81^+	→ 55^+	+ 26)				
$C_5H_9^+$	→ $C_3H_5^+$	+ C_2H_4		24.3	[c]	24.3
(69^+	→ 41^+	+ 28)				

[a] This exact mass measurement was run by Dr. J. H. Beynon, Imperial Chemical Industries, Manchester, England. [b] This extremely strong metastable ion was visible in low-resolution mass spectra without logarithmic transfer recording. [c] Logarithmic transfer recording not run to low enough *m/e* value to observe this metastable ion in xanthate **5**, but undoubtedly occurs by analogy to xanthate **6**.

(13) See also T. H. Kinstle and R. E. Stark, *J. Org. Chem.*, **32**, 1318 (1967).

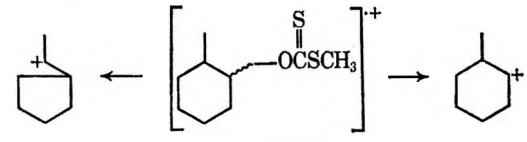
(14) The compound was adsorbed on activated charcoal and introduced using the direct probe inlet into the TO-4 ion source (heated only by the filament current to *ca.* 70°) of the Atlas CH-4 mass spectrometer. A similar technique using molecular sieves has been employed by E. Schumacher and R. Taubenest, *Helv. Chim. Acta*, **49**, 1439 (1966).

the metastable ions[15] and the transitions to which they correspond[16] for these compounds. For comparison purposes, the cold ion source spectrum of the one aromatic S-methyl xanthate, phenyl-S-methyl xanthate (**9**), previously reported[17] from our laboratory, is shown in Figure 5.

Comparison of the 70-eV mass spectra of xanthates **5** and **6** with that (Figure 2) of 1-methyl- (or 3-methyl-) 1-cyclohexene (the expected products if a 1,2-hydrogen abstraction is operative) shows that there is a qualitative correspondence in the region *m/e* 40–96 with the exception of heteroatom-containing fragments[16] at *m/e* 91, 47, and 45 and a peak at *m/e* 69 ($C_5H_9^+$).[18,19] The quantitative differences are those which would be predicted (see Table I) for ions known to arise through further breakdown of the *m/e* 97 ion.

It is quite pertinent to the subsequent discussion of the mode of thermal *vs.* electron impact induced elimination to observe that, in the spectra (Figures 3 and 4) of xanthates **5** and **6**, no peaks appear at *m/e* 48 and 60 corresponding to ionized methyl mercaptan and carbonyl sulfide, respectively. These are the two stable sulfur-containing moieties which are produced in the thermal Chugaev reaction and, while their absence by no means establishes rigorously the complete absence of thermal processes, it does indicate that pyrolysis in the ion source before passing through the ionizing electron beam does not occur. The mass spectrum of the *cis* xanthate (**5**) was also run under instrumental conditions[20] which should promote the pyrolytic process and was, in fact, virtually superimposable upon those (see Figure 2) of 1-methyl- and 3-methyl-1-cyclohexene, the expected pyrolytic products, with the exception of major fragments at *m/e* 60 ($COS^{\cdot+}$), 48 ($CH_3SH^{\cdot+}$), 47 (CH_3S^+), and 45 ($CHS^{\cdot+}$). The latter two fragment ions are also evident in the cold-source mass spectrum (Figure 3) of xanthate **5**. It is clear, therefore, that Figures 3 and 4 represent true mass spectra of the ionized xanthates and not of some pyrolysis products.

The base peak in the 70-eV mass spectra of both xanthates **5** and **6** is due to the even-electron ion of mass 97 (28.1% Σ_{40} in the former compound and 25.6% Σ_{40} in the latter) having the composition $C_7H_{13}^+$ by high resolution mass spectrometry.[16]



o, *m/e* 97 m, *m/e* 204 n, *m/e* 97

(15) Metastable ions were detected with an Atlas CH-4 mass spectrometer in conjunction with a logarithmic transfer recorder. See R. T. Aplin, H. Budzikiewicz, H. S. Horn, and J. Lederberg, *Anal. Chem.*, **37**, 776 (1965).

(16) The composition of all relevant ions was established by high resolution measurements.

(17) J. B. Thomson, P. Brown, and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 4049 (1966).

(18) The complete mass spectra of the deuterated xanthates and acetates along with interpretations of the important fragmentation pathways will be presented in the dissertation submitted by W. S. B. to the Graduate School, Stanford University, 1967, in partial fulfillment of the requirements for a Ph.D. degree.

(19) Total ion current is reported as percentage of $\Sigma_{40}^{M^+}$ (all peaks).

(20) This spectrum was run on a C.E.C. Model 21-103C mass spectrometer equipped with an all-glass heated inlet system (200°) and the isatron temperature maintained at 250°; ionizing voltage, 70 eV; ionizing current, 50 μA.

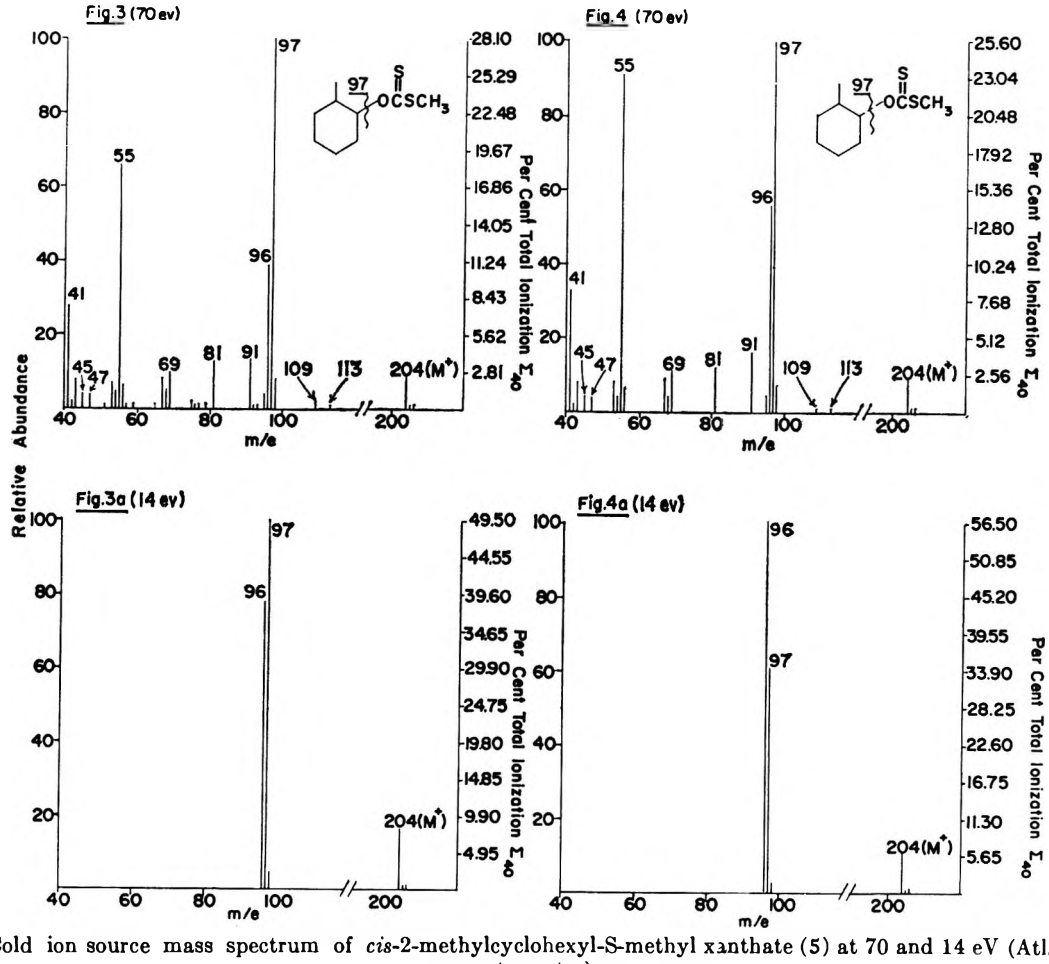


Figure 3.—Cold ion source mass spectrum of *cis*-2-methylcyclohexyl-S-methyl xanthate (5) at 70 and 14 eV (Atlas CH-4 mass spectrometer).

Figure 4.—Cold ion source mass spectrum of *trans*-2-methylcyclohexyl-S-methyl xanthate (6) at 70 and 14 eV (Atlas CH-4 mass spectrometer).

This species corresponds to direct loss of an xanthate radical from the molecular ion (m) and may be represented by the methylcyclohexyl cation n or a rearranged species such as o. In xanthate **9**, the corresponding even-electron species (*m/e* 77) carries only 9.4% Σ_{40} in the 70-eV mass spectrum (Figure 5).

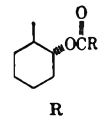
Of particular interest is the fragment ion of mass 96 ($C_7H_{12}^+$) (11.0% Σ_{40} in **5** and 14.3% Σ_{40} in **6**). As will be noted in Table I, at least some of this species arises from expulsion of the elements of xanthic acid from the molecular ion m—the electron impact analog to the thermal Chugaev reaction. In the aromatic xanthate **9** (Figure 5) the analogous elimination process which yields, at least formally, ionized benzyne (*m/e* 76) is much less important (*ca.* 0.3% Σ_{40}).

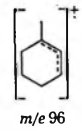
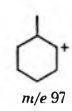
The difference in the behavior of the two xanthate mass spectra (Figures 3 and 4) upon lowering the ionizing voltage is quite striking. Particularly notable in both is that at 14 eV only the molecular ion (*m/e* 204) and the two cleavage ions (*m/e* 96 and 97) remain. As the electron energy is lowered from 70 to 14 eV, the relative intensity of the *m/e* 96 peak compared with that of the *m/e* 97 fragment increases in both xanthate **5** and xanthate **6**; in the latter compound the *m/e* 96 species becomes dominant at 14 eV. However, the differing behavior is more readily apparent if the ratios (1.3 in **5** and 4.8 in **6**) of the difference in the percentage total ion current carried by these two fragments at 70 and 14 eV are considered. The increased ratio is presumably due to the influence of stereochemical factors and is in the direction to be expected for a preferential *cis* mode of hydrogen abstraction.

Before treating the results of deuterium-labeling studies, it is interesting to consider briefly the fate of the complementary "acid" fragment produced in the *m/e* 96 yielding elimination process. In acetate and propionate esters of alcohols having available β hydrogens in which McLafferty rearrangements of the type c → d may occur, the charge is only retained by the oxygenated fragment when a double hydrogen transfer occurs and an acyloxonium species of type p is generated.[8] In higher esters (see Table II), the

TABLE II

SUMMARY OF THE EFFECTS[a] OF THE ACYL SIDE CHAIN LENGTH ON THE VARIOUS CLEAVAGE MODES IN *trans*-2-METHYLCYCLOHEXYL ESTERS



R	$RCO_2H^{\cdot+}$	$RCO_2H_2^+$	 *m/e* 96	 *m/e* 97	Ratio of *m/e* 96 : *m/e* 97
CH_3 (**8**)	...	...	17.5	0.8	21.9
C_2H_5 (**23**)	...	0.5	14.1	2.9	4.9
n-C_3H_7 (**24**)	...	1.1	14.8	4.0	3.7
n-C_4H_9 (**25**)	0.3	1.4	16.0[b]	5.8	2.8
n-C_7H_{15} (**26**)	0.6	1.5	18.4[b]	7.4	2.5

[a] Data from 70 ev spectra, corrected for ^{13}C isotope contributions and reported as $\%\Sigma_{29}$. [b] Denotes base peak of spectrum.

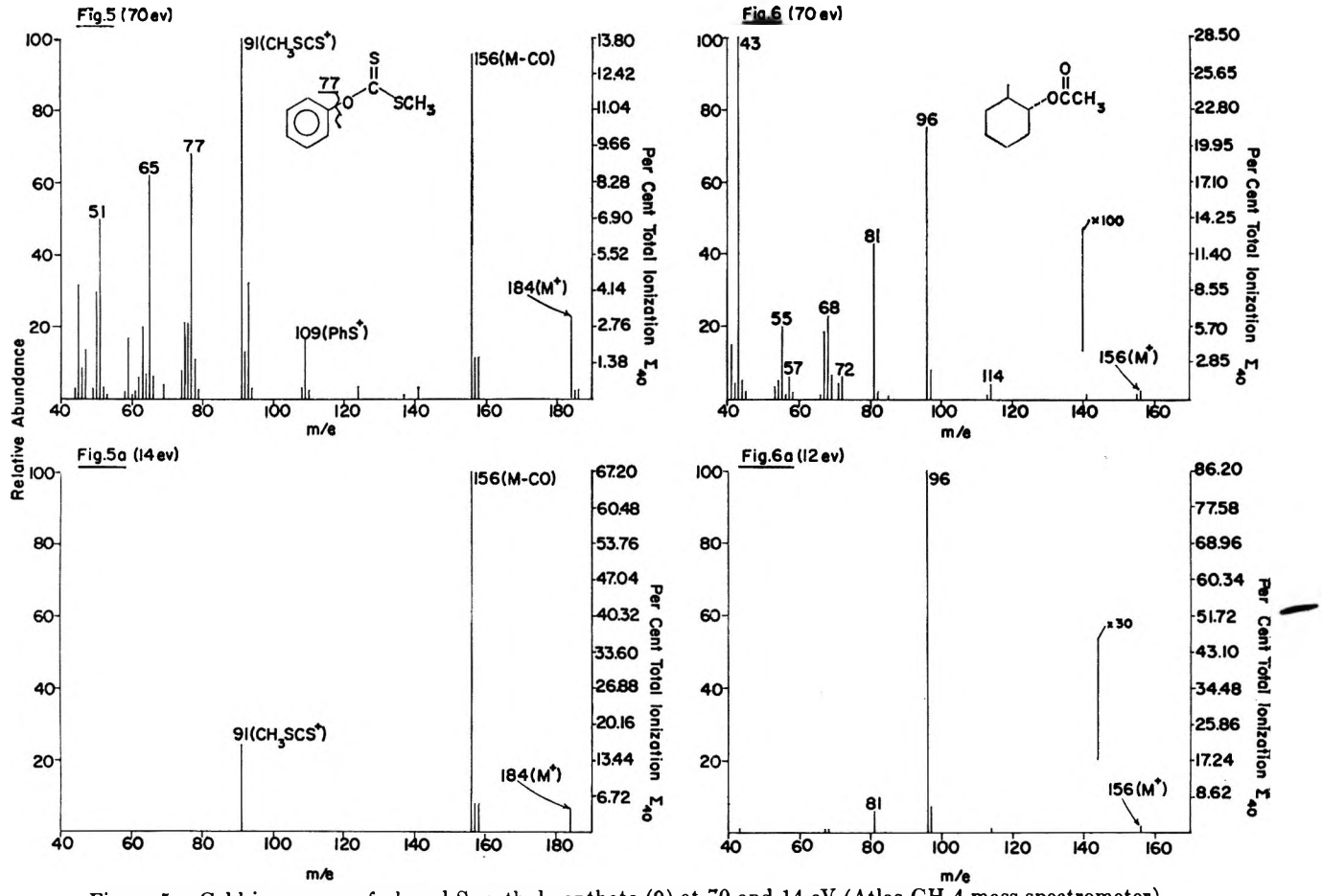
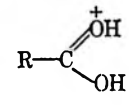


Figure 5.—Cold ion source of phenyl-S-methyl xanthate (9) at 70 and 14 eV (Atlas CH-4 mass spectrometer).
Figure 6.—Mass spectrum of *trans*-2-methylcyclohexyl acetate (8) at 70 and 12 eV (Atlas CH-4 mass spectrometer).

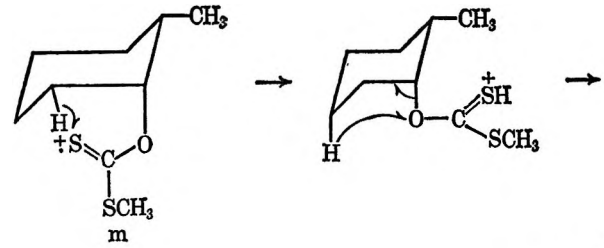
ionized acid itself bears an increasingly greater portion of the ion current; however, species of type p still carry the greater proportion.



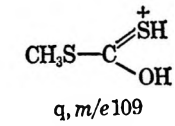
p, R = CH_3 or C_2H_5

Likewise, in xanthates **5** and **6** no species corresponding to the ionized xanthic acid molecule (*m/e* 108) is to be found in the low-resolution mass spectra; however, a peak at *m/e* 109 (Σ_{40} 0.3%) is visible in both spectra and presumably corresponds to the ionized protonated acid form (q) analogous to ion p. Shifts of this peak observed in the deuterated xanthates are consistent with this view; however, owing to the small magnitude of the peak, no precise quantitative calculations concerning the source of the second transferred hydrogen could be made. It appears, however, that most arises from C-3 and C-5 of the 2-methylcyclohexyl system, since little if any comes from compounds specifically labeled with deuterium at C-1, C-2, C-2 plus C-6, or C-4. This apparent loss of a γ-hydrogen atom is analogous to the similar process noted in open-chain esters[8b] in the formation of the protonated acid species (p, R = C_2H_5) and a mechanism of the type m → q may be operative.

In Table III are summarized the mass spectrometric data obtained for the specifically deuterated xanthates (**10**–**19**) synthesized to establish the stereochemical nature and course of the *m/e* 96 forming process and in Table IV the percentage of hydrogen loss from each



m



q, *m/e* 109

ring position is noted for xanthates **5** and **6**. For comparison purposes, Table V presents an account of the pyrolytic results[21] obtained for the 2-d_1-labeled and unlabeled materials.

Inspection of the data summarized in Table IV reveals that the electron impact induced elimination proceeds primarily by the 1,2 mode, analogous to that previously found for cyclic acetates.[12,22] Particularly striking is the high specificity toward the tertiary center which leads to 90% abstraction of the tertiary hydrogen atom at C-2, whereas only 2% proceeds with elimination of the equally available (*cis*) secondary hydrogen at C-6. This is in contrast[21] to the thermal process (Table V) in which a combination of statistical and thermodynamic factors dictates the formation of the more highly substituted 1-methyl-1-

(21) W. S. Briggs and C. Djerassi, *J. Org. Chem.*, **33**, 1625 (1968).
(22) C. G. Macdonald, J. S. Shannon and G. Sugowdz, *Tetrahedron Lett.*, 807 (1963).

TABLE III

SUMMARY OF MASS SPECTROMETRIC DATA OBTAINED FOR DEUTERATED 2-METHYLCYCLOHEXYL-S-METHYL XANTHATES

Compound[b]	Isotopic purity,[c] % d_0	d_1	d_2	d_3	Ionizing conditions[a]	Peaks in group m/e 95–100[d] 95	96	97	98	99	100	Percentage of one deuterium loss in formation of M − 108 fragment[e]
trans-d_0 (**6**)	100	...	...	...	A	2.6	37.1	60.3	...	...	...	...
					B	...	65.2	34.8	...	...	...	...
					C	3.0	49.8	47.2	...	...	...	...
trans-1-d_1 (**10**)	1	99	...	...	C	1.4	4.1	46.6	47.9	...	...	5
trans-2-d_1 (**11**)	2	98	...	...	A	...	35.2	5.7	59.1	...	...	90
					B	...	56.4	6.3	37.3	...	...	90
trans-2,6,6-d_3 (**12**)	...	...	3	97	A	...	...	0.9	33.6	2.7	62.8	92
trans-ring Me-d_3 (**13**)	...	1	7	92	C	...	...	...	3.4	52.5	44.1	0
trans-S-Me-d_3 (**14**)	...	...	...	100	C	3.6	49.1	47.3	...	...	...	100% loss of 3
cis-d_0 (**5**)	100	...	...	...	A	2.8	28.2	69.0	...	...	...	...
					D	...	33.4	66.6	...	...	...	...
cis-1-d_1 (**15**)	1	99	...	...	A	1.4	1.8	27.0	69.8	...	...	1
cis-2-d_1 (**16**)	5	95	...	...	A	0.5	11.2	18.6	69.7	...	...	32
					D	...	12.4	25.4	62.2	...	...	37
cis-4,4-d_2 (**17**)	...	3	97	...	A	...	...	3.1	24.4	72.5	...	2
cis-6,6-d_2 (**18**)	2	2	90	6	A	0.7	0.7	7.6	13.1	77.9	...	32
cis-2,6,6-d_3 (**19**)	2	4	5	89	A	...	1.0	2.6	21.8	4.2	70.4	84

[a] Ionizing conditions: A, cold source,[14] 70 eV; B, same as A, 14 eV; C, heated gas cartridge inlet system (70°), Atlas CH-4, ion source temperature, 145°, 70 eV; D, same as A, 16 eV. [b] See Experimental Section. [c] All isotopic purities calculated from molecular ion region of spectrum and considered reproducible to ±1%. [d] These values have been corrected in the best manner possible for isotopic contaminants and for ^{13}C isotope contributions and are reported as $\%\Sigma_{95}^{100}$. [e] Values are the average of five to twenty calculations and are considered reproducible to ±2%.

TABLE IV

SUMMARY OF POSITIONAL SPECIFICITY OF HYDROGEN LOSS IN FORMATION OF *m/e* 96 FRAGMENT IONS IN XANTHATE MASS SPECTRA

Compound	Percentage[b] of hydrogen loss from various positions: Ring CH_3	C-1	C-2	C-4	C-6	Unaccounted for[a]
cis (**5**)	*a*	1	47	2	37	13
trans (**6**)	0	*a*	90	*a*	2	5

[a] See text. [b] These figures are the weighted averages of results obtained at both high (70 eV) and low (16 and 14 eV) electron energies, since little change is noted in the per cent transfer from any given position with changing ionizing energy (see Table III).

TABLE V

SUMMARY OF PYROLYTIC STUDIES ON 2-METHYLCYCLOHEXYL-S-METHYL XANTHATES AND ACETATES[a]

Compound	Percentage of olefin mixture[b]	
trans-d_0 (**6**)	65	35
cis-d_0 (**5**)	29	71
trans-2-d_1 (**11**)	55 (>98% d_0)	45 (>97% d_1)
cis-2-d_1 (**16**)	28 (56% d_0, 44% d_1)	72 (15% d_0, 85% d_1)
trans-d_0 (**8**)	56	44
cis-d_0 (**7**)	9	91
trans-2-d_1 (**28**)	41 (>97% d_0)	59 (100% d_1)
cis-2-d_1 (**34**)	5 (22% d_0, 78% d_1)	95 (100% d_1)

[a] Values reported are those obtained for pyrolysis in seasoned stainless steel at 250° (xanthates) and 400° (acetates). For a full discussion of pyrolysis studies on these compounds, see ref 22. [b] These values are corrected for the contribution of isotopic contaminants and any significant quantities of the isomeric materials present.

cyclohexene by tertiary hydrogen abstraction only 65–66% of the time.

From the mass spectral data for the labeled xanthates (Table III), values for the π and Γ deuterium isotope effects[23–25] may be calculated.[26] The π value of 0.64 found for the *cis* xanthate (**5**) is somewhat lower than the π value of 0.80 recently measured[24] in this laboratory for the McLafferty rearrangement process in the thione ester **20**, as would be predicted

(23) F. H. Field and J. L. Franklin, "Electron Impact Phenomena and the Chemistry of Gaseous Ions," Academic Press Inc., New York, N. Y., 1957, pp 204–217.

(24) (a) J. K. MacLeod and C. Djerassi, *Tetrahedron Lett.*, 2183 (1966); and (b) J. K. MacLeod and C. Djerassi, *J. Amer. Chem. Soc.*, **89**, 5182 (1967).

(25) P. Natalis, *Bull. Soc. Chim. Belges*, **73**, 389 (1964).

(26) By making the initial reasonable assumptions that the elimination process is unimolecular and that the isotope effects (both primary and secondary) are "additive," expressions of the following type may be derived for *cis*-2-methylcyclohexyl-*S*-methyl xanthate **5** from data in Table III

$$0.84 = P\Gamma^2\gamma[\%\ H(2)] + P\Gamma_\alpha\Gamma\gamma[\%\ H(6)] \quad (1)$$
$$0.35 = P[\%\ H(2)] \quad (2)$$
$$0.32 = P\Gamma_\alpha[\%\ H(6)] \quad (3)$$
$$P = \pi\Gamma \quad (4)$$

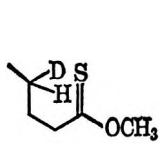
where P is the primary kinetic deuterium isotope effect defined as (probability of losing D in the deuterated compound)/(probability of losing H in the nondeuterated compound); $\Gamma_{\alpha(\text{or}\gamma)}$ is the secondary kinetic deuterium isotope effect defined as (probability of losing H in the deuterated compound)/(probability of losing H in the nondeuterated compound), with the deuterium atom at the same (α) (C-6) or γ position; % H(2) and % H(6) are the percentages of hydrogen loss from these two positions in the nondeuterated compound; and π is defined[22] as (probability of losing D in the deuterated compound)/(probability of losing H in the deuterated compound). By contrast to solution chemistry where secondary isotope effects (k_D/k_H) [see E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963)] are generally less than unity, mass spectral processes exhibit Γ effects from all positions[25] which are in the range 1.1–1.2. By combining eq 2 and 3 with eq 1, a quadratic expression (5) in terms of Γ_γ results and this upon solution yields a value for Γ_γ of 1.16, in good agreement with those found in other systems. Since Γ_α and

$$0.35\Gamma^2_\gamma + 0.32\Gamma_\gamma - 0.84 = 0 \quad (5)$$
$$\Gamma_\gamma = 1.16$$

Γ_γ are generally of approximately the same magnitude, a value of $\Gamma_\alpha = 1.16$ may be assumed. Assuming that the total hydrogen loss from the 2 and 6 positions is indeed 84%, values of % H(2), % H(6), P, and π may be calculated from eq 2, 3, and 4.

$$\%\ H(2) = 47\%$$
$$\%\ H(6) = 37\%$$
$$P = 0.74$$
$$\pi = 0.64$$

by analogy[24] to other cases in which an ether oxygen was introduced into the rearranging side chain. By contrast, *trans* xanthate **6** yields a π effect of nearly unity. The possible mechanistic implications of these isotope effect data will be discussed below.



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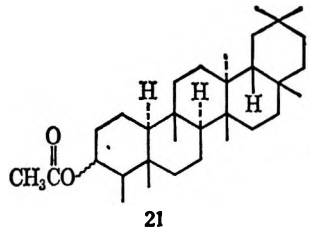
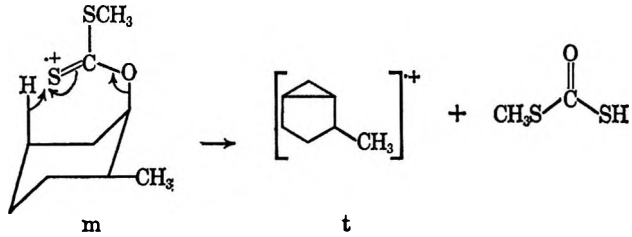


21

As opposed to the purely 1,2 mode of elimination in the pyrolytically induced reaction, the electron impact induced elimination of xanthates also proceeds to a small extent *via* 1,3 and 1,4 modes as is evidenced by the data in Table IV. Such processes have been previously noted in monocyclic[12,22] and triterpene[22] acetates and may be dominant when structural or stereochemical factors prevent the preferred 1,2-elimination process; thus in friedelan-3-ol acetate (**21**) deuterium labeling has shown[22] that none of the acetic acid produced originates from a 1,2-elimination process. While the mass spectra of the *cis*-ring-methyl-d_3 and *trans*-4,4-d_2 xanthates were not carried out, inspection of models gives no indication of reasons to expect increased elimination in these compounds compared with that of their C-2 epimers and in the subsequent discussion the percentage of hydrogen loss from each of these positions may be assumed to be equal to or less than that from the same position in the epimeric series. In Table IV, the last column presumably reflects the joint contribution of 1,3-elimination processes from C-3 and C-5 and isotope effects. Assuming the latter effects to be of approximately the same order of magnitude in both series, it is apparent that the amount of 1,3-elimination process in the *cis* xanthate (**5**) is at least twice as great as in isomer **6**. This elimination may be visualized as proceeding through a five- or seven-membered transition state of which m → t is representative.

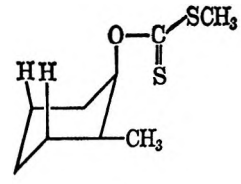


m **t**

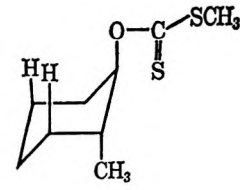
It is noteworthy that while ground-state conformational free-energy arguments[27] derived from solution chemistry are most certainly not directly applicable to the excited states of organic molecules in gas phase reactions, such as mass spectral fragmentations, the results obtained for the relative importance of the 1,3-elimination mode in the two 2-methylcyclohexyl-S-methyl xanthates correlate qualitatively with predictions made using ground-state "A" values.[27,28]

(27) See, for example, E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 234–239.

Such calculations predict that at 80° slightly over 80% of the *cis* xanthate should exist in chair conformer (**5′**) with the xanthate function axial, the required orientation for 1,3 elimination to take place, whereas only 5% of xanthate **6** should exist in the corresponding chair conformer (**6′**) at this temperature.



5′

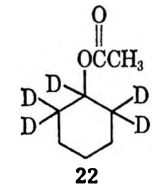


6′

Consideration of the required boat forms gives qualitatively the same result. It would be predicted in the above manner that the 1,4-elimination process would also be favored in xanthate **5** over that in xanthate **6**, but the required spectrum of 4,4-d_2-*trans* isomer was not available for comparison.

2-Methylcyclohexyl Acetates and Higher Esters.— Acetates, as one of the most common derivatives of alcohols employed in synthetic organic chemistry, have been examined previously in terms of mass spectrometric behavior.[8a,22,29,30] These studies indicated that major fragment ions result through initial expulsion of the elements of acetic acid from the molecular ion with charge retention on the resulting hydrocarbon fragment[8a,22,29] when the alcoholic side chain is greater than ethyl.

In straight-chain acetates[8a] and propionates,[8b] the course of this elimination was found by deuterium-labeling studies to be about equally divided between 1,3 (45%, clearly electron impact induced) and 1,2 (55%, either electron impact or possibly thermally induced) processes. In monocyclic acetates, by far the most predominant mode of elimination is 1,2 in nature.[12,22] In fact we found that in 1,2,2,6,6-d_5-cyclohexyl acetate (**22**) 83% of the elimination process



22

results in loss of CH_3CO_2D (the result of the 1,2 mode) whereas 17% results in loss of CH_3CO_2H (1,3 and 1,4 modes). This percentage loss is found to be virtually independent of the electron energy employed in the range 12–70 eV.

It was of interest, therefore, to examine this elimination process for the C-2 epimeric methylcyclohexyl acetates **7** and **8**, in which the availability of specifically deuterated substrates might allow conclusions to be drawn regarding the sensitivity of this process to the *cis* or *trans* orientation of the eliminated β-

(28) Assuming that the conformational "A" value of the xanthate function is roughly equal to that of the acetate group ("A" = *ca.* 0.6 kcal/mol), the governing factor in determining this value being the *gauche* interaction with a C–O bond in both cases (see ref 27).

(29) For recent examples, see (a) ref 12; (b) E. v. Sydow, *Acta Chem. Scand.*, **19**, 2083 (1965); (c) V. I. Zaretskii, N. S. Wulfson, V. G. Zaikin, V. N. Leonov, S. N. Ananchenko, and I. V. Torgov, *Tetrahedron Lett.*, 347 (1966); and (d) S. J. Cristol, R. A. Sanchez, and T. C. Morrill, *J. Org. Chem.*, **32**, 2738 (1966).

(30) K. Biemann and J. Seibl, *J. Amer. Chem. Soc.*, **81**, 3149 (1959).

hydrogens with respect to the departing acetate function. Also, it was thought pertinent to examine the effect of lengthening the acid side chain upon the course of this elimination.

The low-resolution electron impact mass spectra of acetates **7** and **8** were run at 70 and 12 eV and, as the spectra of the two compounds are virtually superimposable at all electron energies, only those of the *trans* isomer (**8**) are shown (Figure 6). The photoionization[31] mass spectrum (Figure 7) of **8** was also available for comparison and corresponds well to the low-voltage electron impact spectrum. In Table VI are summarized the metastable ion transitions noted in the mass spectra of acetates **7** and **8**.

TABLE VI

METASTABLE TRANSITIONS AND ELEMENTAL COMPOSITIONS OF FRAGMENTS FROM 2-METHYLCYCLOHEXYL ACETATES

Transition	Calcd	Found for *cis* acetate (**7**)	Found for *trans* acetate (**8**)
$C_9H_{16}O_2^{\cdot+} \rightarrow C_7H_{12}^{\cdot+} + C_2H_4O_2$	59.0	59.0	59.0
($156^+ \rightarrow 96^+$ 60)			
$C_7H_{14}O^{\cdot+}$ [a] $\rightarrow C_4H_8O^{\cdot+} + C_3H_6$	45.4	45.4	45.5
($114^+ \rightarrow 72^+ + 42$)			
$C_7H_{14}O^{\cdot+} \rightarrow C_4H_7O^+ + C_3H_7$	44.2	44.3	44.2
($114^+ \rightarrow 71^+ + 43$)			
$C_7H_{14}O^{\cdot+} \rightarrow C_3H_5O^+ + C_4H_9$	28.4	28.3	28.3
($114^+ \rightarrow 57^+ + 57$)			
$C_7H_{13}^+ \rightarrow C_5H_9^+ + C_2H_4$	49.1	49.2	49.1
($97^+ \rightarrow 69^+ + 28$)			
$C_7H_{13}^+ \rightarrow C_5H_8^+ + C_2H_5$	47.6	47.5	47.5
($97^+ \rightarrow 68^+ + 29$)			
$C_7H_{13}^+ \rightarrow C_4H_7^+ + C_3H_6$	31.2	31.3	31.2
($97^+ \rightarrow 55^+ + 42$)			
$C_7H_{12}^{\cdot+} \rightarrow C_6H_9^+ + CH_3$	68.3[b]	68.4	68.3
($96^+ \rightarrow 81^+ + 15$)			
$C_7H_{12}^{\cdot+} \rightarrow C_5H_8^{\cdot+} + C_2H_4$	48.2	...	48.2[c]
($96^+ \rightarrow 68^+ + 28$)			
$C_7H_{12}^{\cdot+} \rightarrow C_5H_7^+ + C_2H_5$	46.7	46.8	46.8
($96^+ \rightarrow 67^+ + 29$)			
$C_6H_9^+ \rightarrow C_4H_7^+ + C_2H_2$	37.3	37.2	37.2
($81^+ \rightarrow 55^+ + 26$)			
$C_5H_9^+ \rightarrow C_3H_5^+ + C_2H_4$	24.3	24.4	24.4
($69^+ \rightarrow 41^+ + 28$)			
$C_5H_7^+ \rightarrow C_3H_5^+ + C_2H_2$	25.1	25.2	25.2
($67^+ \rightarrow 41^+ + 26$)			

[a] See footnote *a* in Table I. [b] See footnote *b* in Table I. [c] This metastable ion was found in the photoionization mass spectrum of acetate **8** (see Table I, footnote *a*).

Just as previously noted for the xanthates **5** and **6**, there exists a qualitative correspondence of the fragment ion peaks below *m/e* 100 in the 70-eV spectrum (Figure 6) of acetate **8** with those of the expected ionized olefinic products, 1-methyl- (or 3-methyl-) 1-cyclohexene (Figure 2), with additional peaks at *m/e* 72, 71, 69, 58, 47, and 43. With the exception of the *m/e* 69 fragment ($C_5H_9^+$) which arises through expulsion of ethylene from the even-electron species of mass 97 and whose genesis is supported by the appropriate metastable ion at *m/e* 49.1 (Table VI), these latter ions are oxygen containing. Except for

(31) We wish to thank Dr. J. H. Beynon (Table I, footnote *a*) for the determination of this spectrum. Ionizing conditions are as follows: A.E.I. MS-9 mass spectrometer equipped with a glass inlet system and hydrogen discharge photon lamp; ion source temperature, 50°; ionizing energy, 10.19 eV (Lyman-α line of hydrogen). See J. H. Beynon, A. E. Fontaine, D. W. Turner, and A. E. Williams, *J. Sci. Instru.*, **44**, 283 (1967).

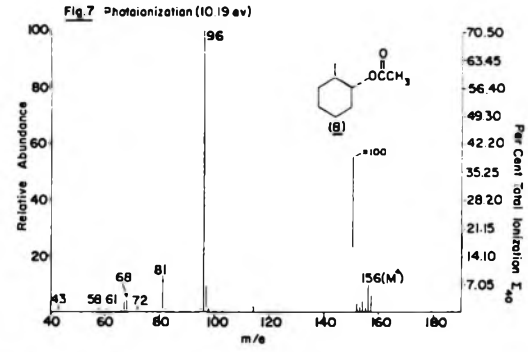
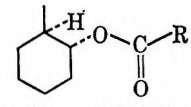


Figure 7.—Photoionization mass spectrum of *trans*-2-methylcyclohexyl acetate, 10.19 eV.

the well-known acetylium ion of mass 43, these arise from cleavages in the alcoholic grouping.[18]

The higher esters of *trans*-2-methylcyclohexanol, *viz.*, *trans*-2-methylcyclohexyl propionate (**23**), butyrate (**24**), valerate (**25**), and octanoate (**26**), behave in a qualitatively similar manner to the acetate (**8**) in respect to cleavages in the alcoholic grouping. Cleavages in the acyl side chain in such aliphatic esters have been well documented in the literature[8b,32] and suffice it to note that esters **23**–**26** behave in the expected manner. Of particular interest in the present study is the observation (Table II) that in the mass spectra of these esters the proportion of the total ion current carried by the even electron ion of mass 97 relative to that borne by that of mass 96 regularly increases as the acyl carbon chain is lengthened.



23, R = $-CH_2CH_3$
24, R = $-(CH_2)_2CH_3$
25, R = $-(CH_2)_3CH_3$
26, R = $-(CH_2)_6CH_3$

In Table VII are collected the mass spectral data in the *m/e* 95–100 region for the deuterium-labeled esters, while in Table VIII are summarized the positional specificities of hydrogen loss in the formation of the *m/e* 96 peak. It will be noted that the percentage hydrogen loss from any one position is virtually independent (Table VII) of the experimental conditions (hot or cold ion source, high or low energy electrons, photoionization, etc.) and this, coupled with the observed metastable ion at *m/e* 59.0 in acetates **7** and **8** (Table VI) corresponding to the direct loss of acetic acid from the molecular ion, would suggest that in this case a purely electron impact induced elimination process is being observed. Also supporting this view are the differences to be noted in the site specificities of the pyrolytic[21] (Table V) and mass spectrometrically induced (Table VIII) elimination processes.

Most noteworthy are the small differences (Table VIII) in behavior exhibited by the *cis* and *trans* esters as compared with those of the corresponding xanthates. Also apparent is the independence of the specificity of elimination upon acyl chain length, as is evidenced by the nearly identical data obtained for the *trans* acetate (**8**) and the *trans* valerate (**25**).

(32) (a) Chapter 4 in ref 7; (b) R. Ryhage and E. Stenhagen in "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press Inc., New York, N. Y., 1963, Chapter 9.

TABLE VII

SUMMARY OF MASS SPECTROMETRIC DATA OBTAINED FOR DEUTERATED 2-METHYLCYCLOHEXYL ESTERS

Compound[b]	Isotopic purity,[c] % d_0	d_1	d_2	d_3	Ionizing[a] conditions	Peaks in group m/e 95–100[d] 95	96	97	98	99	100	Percentage of one deterium loss in formation of M − RCO_2H fragment[e]
R = CH_3												
trans-d_0 (8)	100	...	...	...	E	11.1	84.4	4.5	...	...	...	...
					C	9.6	86.7	3.6	...	...	...	...
					A	9.3	83.7	7.0	...	...	...	...
					F	11.9	82.7	5.4	...	...	...	...
					G	...	98.8	1.2	...	...	...	...
					H	1.0	96.8	2.2	...	...	...	...
trans-1-d_1 (27)	1	99	...	...	C	1.6	11.7	83.9	2.8	...	...	5
trans-2-d_1 (28)	2	98	...	...	E	2.1	38.5	53.9	5.5	...	...	35
					C	2.2	35.7	57.1	5.0	...	...	33
					A	5.8	33.2	55.3	5.7	...	...	36
					F	3.6	39.2	49.6	7.6	...	...	37
					G	...	30.4	67.9	1.7	...	...	32
					H	...	34.3	62.8	2.9	...	...	35
trans-4,4-d_2 (29)	...	3	97	...	C	...	3.2	9.9	83.3	3.6	...	4
trans-6,6-d_2 (30)	...	...	94	6	E	..	3.0	45.4	48.3	3.3	...	44
trans-2,6,6-d_3 (31)	...	...	3	97	C	..	0.7	2.3	79.1	13.7	4.2	84
trans-ring Me-d_3 (32)	...	1	7	92	E	..	...	0.9	9.9	84.9	4.3	0
cis-d_0 (7)	100	...	...	...	E	10.3	85.2	4.5	...	...	...	...
					C	8.8	87.4	3.8	...	...	...	...
cis-1-d_1 (33)	1	99	...	...	C	1.4	15.2	79.9	3.5	...	...	9
cis-2-d_1 (34)	5	95	...	...	E	2.2	43.6	50.8	3.4	...	...	38
cis-4,4-d_2 (35)	...	3	97	...	C	0.7	3.1	10.5	81.4	4.3	...	6
cis-6,6-d_2 (36)	2	2	90	6	C	...	...	42.1	57.9	...	...	37
cis-2,6,6-d_3 (37)	2	4	5	89	C	...	...	...	78.2	18.3	3.5	80
R = $-(CH_2)_3CH_3$												
trans-d_0 (25)	100	...	...	...	E	5.0	72.0	23.0	...	...	...	...
trans-1-d_1 (38)	1	99	...	...	E	0.7	6.6	72.3	20.4	...	...	4
trans-2-d_1 (39)	2	98	...	...	E	1.7	30.0	42.1	26.2	...	...	39
trans-6,6-d_2 (40)	...	...	94	6	E	...	2.0	36.3	37.8	23.9	...	47
trans-2,6,6-d_3 (41)	...	...	3	97	E	...	...	1.2	64.0	12.6	22.2	83

[a] A–D, see footnote *a*, Table III; E, same as C, ion source temperature, 175°; F, see ref 20; G, see ref 31; H, same as C, 12 eV. [b] See footnote *b*, Table III. [c] All isotopic contents were calculated from the molecular ion region of the corresponding S-methyl xanthates (Table III) and considered to be reproducible to ±1%. [d] See footnote *d* in Table III. [e] See footnote *e* in Table III.

TABLE VIII

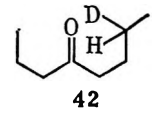
SUMMARY OF POSITIONAL SPECIFICITY OF HYDROGEN LOSS IN THE FORMATION OF *m/e* 96 FRAGMENT IONS IN ESTER MASS SPECTRA

Compound	Percentage[c] of hydrogen loss from various positions: Ring $-CH_3$	C-1	C-2	C-4	C-6	Unaccounted for
R = CH_3						
cis (7)	*a*	9	42	5	37	7
trans (8)	0	5	38	3	47	7
R = $-CH_2(CH_2)_2CH_3$						
trans (25)	*b*	4	38	*b*	45	10

[a] These labeled compounds were not available for comparison; however, inspection of models gives little reason to expect greater loss from the respective positions than recorded for the epimeric (*a*) or stereochemically identical (*b*) series. [b] Same as footnote *a*. [c] Reported values are the averages of numerous measurements at high and low electron energies. Minor (if any) changes were evident in the percentage loss of hydrogen from any given position in the range 12–70 eV.

The differences in positional specificity, albeit small, are interesting, since they are in the opposite direction to those expected for a preferential *cis* mode of elimination.

From the data in Table VII, π isotope effects[23–25] for the electron impact induced 1,2-elimination process may be calculated[26] in the acetates **7** (1.0) and **8** (0.84). These values are somewhat lower (greater isotope effect) than the π-effect value of 1.0 measured for the McLafferty rearrangement process[24] in 3-heptanone-6-d_1 (**42**), again in accord with expectations when an ether oxygen is introduced into the rearranging side chain.[24]



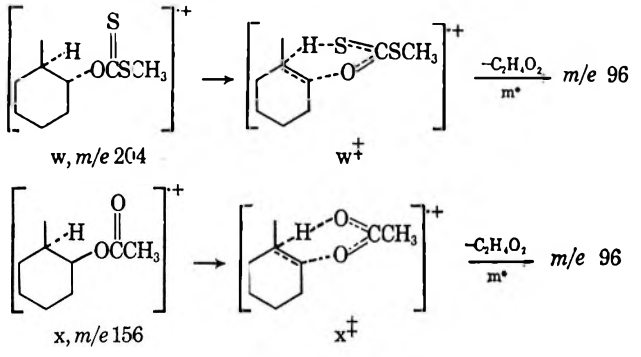
42

From the kinetic isotope effect and site specificity data (Tables IV and VIII) for compounds **5–8**, some information may be derived concerning the mechanism of the electron impact induced elimination process in 2-methylcyclohexyl-S-methyl xanthates and esters. First, it is important to note that in both the xanthate and acetate series, the calculated π-effect values are consistent with less complete hydrogen transfer (and resulting greater asymmetry in the activated complex[33]) when the tertiary hydrogen is in a *trans* relationship to the departing oxygenated function as compared to a *cis* relationship (see Figure 8), pro-

(33) F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).

vided that a more complete transfer of hydrogen to thione sulfur than to carbonyl oxygen is assumed. Second, the small magnitudes of the π effects in all cases may be an indication of the low magnitude of the maximum isotope effect possible in such mass spectral processes, as it is difficult to imagine that two such closely related eliminations require both virtually complete (xanthates) and incomplete (acetates) transfer of hydrogen in the activated complex. The large proportion of the 1,2-elimination process which is directed toward the tertiary center in xanthate **6** is in accord with a mechanism which requires nearly complete transfer of hydrogen to thione sulfur, as the stability of tertiary *vs.* secondary radicals at carbon is well known[34] and the thermodynamic stability of the incipient ionized 1-methyl-1-cyclohexene should be slightly greater than that of incipient ionized 3-methyl-1-cyclohexene.

Thus, the observed isotope effect data for both xanthates **5** and **6** and acetates **7** and **8** appear consistent with a cyclic mechanism such as that previously suggested[21] for the mass spectral elimination process in monocyclic acetates and analogous to that currently accepted[9] in the pyrolysis of esters and xanthates. However, as opposed to the nearly symmetrical disposition of the itinerant hydrogen envisaged in the activated complex of the pyrolytic process,[9] the degree of hydrogen transfer appears to be much more strongly dependent on the nature of the receptor atom in the electron impact case, leading to unsymmetrical extremes (such as w‡ and x‡) of the activated complex (see also Figure 8).



Concerning the stereochemical course of the electron impact induced elimination process, very little can be said in the ester cases owing to the nearly identical amounts of elimination toward the tertiary center regardless of the stereochemical relationship of this hydrogen to the ester function. The failure to observe any specificity may be attributed to ring conformational freedom and is in accord with the observation that the amides[11a] and methyl esters[11b] of the *cis*- and *trans*-2,2,6-trimethylcyclohexylacetic acids (**43** and **44**) give nearly equal quantities of the respective McLafferty rearrangement ions (y and z) regardless of their stereochemical nature. The higher π isotope effect (1.0) found for the *cis* acetate (**7**) compared with that (0.84) calculated for the *trans* isomer (**8**) and the greater percentage of the total elimination process (85 *vs.* 79%) which goes by the 1,2 mode in the latter compound do, however, tempt one to

(34) See, for example, J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 422, 423.

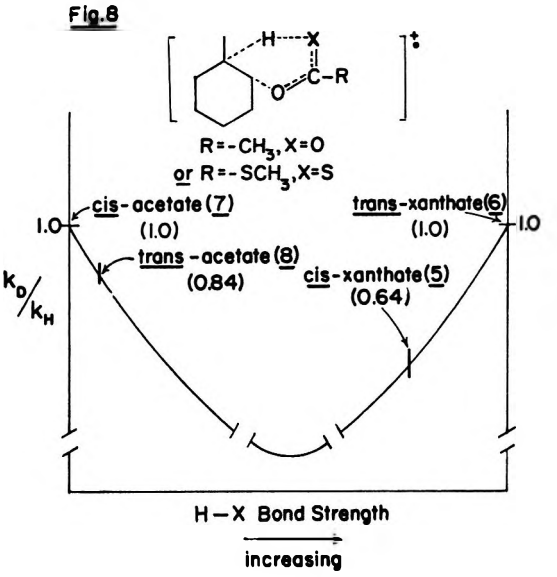
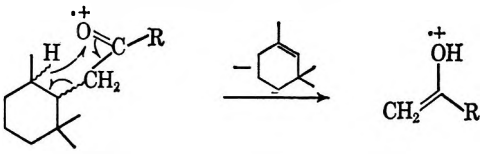


Figure 8.—Diagram relating position of migrating hydrogen in the activated complex to the expected π-isotope effect for 2-methylcyclohexyl-S-methyl xanthates and acetates.

speculate that the 1,2-elimination process is more favorable when the departing hydrogen and oxygenated function are in a *cis* relationship.



43 (*cis*), R = $-NH_2$ or $-OCH_3$ y, R = $-NH_2$; *m/e* 74
44 (*trans*), R = $-NH_2$ or $-OCH_3$ z, R = $-OCH_3$; *m/e* 59

In the xanthates, however, a greater degree of stereochemical specificity is evident. Site specificity data at the tertiary center (Table V) and π isotope effect data [0.64 for **5** (*trans* hydrogen), 1.0 for **6** (*cis* hydrogen)] are consistent with a preferred *cis* mode of elimination in this series, analogous to that found[9] in the thermal case.

Experimental Section[35]

cis-2-Methylcyclohexyl-S-methyl Xanthate (5). Procedure A.—Practical grade 2-methylcyclohexanol[36] was subjected to

(35) All melting points were determined on a Thomas–Hoover Unimelt apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord spectrophotometer. All preparative and analytical gas chromatography was performed on a Varian Aerograph Model 202 instrument equipped with the various columns noted in this section. Nmr spectra were measured by Dr. Lois J. Durham and Mr. Donald McMillan on a Varian A-60 instrument, employing deuteriochloroform as solvent and tetramethylsilane (δ 0.00 ppm) as internal reference. Mass spectra recorded with a Consolidated Electrodynamics Corp. Model 21-103C mass spectrometer[20] were run by Messrs. John Smith and Nelson Garcia. Mass spectra measured on an Atlas CH-4 mass spectrometer were recorded by Dr. A. M. Duffield, Dr. J. K. MacLeod, and Mr. Robert Ross. This mass spectrometer is equipped with a TO-4 ion source and instrumental conditions employed for the various measurements were as summarized in ref 14 and footnote *a* in Tables III and VII. The ionizing current for all spectra determined with the heated inlet system on this instrument was 10 μa. Mass spectra and high-resolution data recorded with an A. E. I. MS-9 mass spectrometer were determined by Mr. Robert Ross. The sample was inserted using the heated inlet system with the ion source temperature at 200°. The ionizing energy for all instruments was 70 ev unless otherwise noted. All microanalyses were performed by Messrs. E. Meier and J. Consul. Isotopic contents of all deuterated derivatives are summarized in Tables III and VII of the text. All low-voltage mass spectra are expressed at nominal electron volts, with 14 eV on the direct probe inlet corresponding roughly to 12 eV on the gas cartridge inlet on the Atlas CH-4.

(36) Eastman Kodak No. P1132, containing 50% *cis* and 50% *trans* isomers, by gas chromatographic analysis, purchased from Eastman Organic Chemicals, Distillation Products Industries, Rochester, N. Y.

preparative gas chromatography on a 20% glycerol column (20 ft × 0.25 in.) at 97° (conditions A). The isomer having the shorter retention time was collected and found to be identical in every respect with a sample of authentic *cis*-2-methylcyclohexanol prepared by the catalytic hydrogenation of 2-methylcyclohexanone using the procedure of Hückel and Hubele.[37] Utilizing the method of Djerassi, *et al.*,[38] 100 mg of this alcohol (**45**) was converted into the corresponding S-methyl xanthate in *ca.* 70% yield by treating the alcoholate salt in refluxing benzene sequentially with a slight excess of carbon disulfide and methyl iodide. The crude xanthate was purified by gas chromatography on a 15% Apiezon L column (5 ft × 0.25 in.) at 160° (conditions B): $\lambda_{max}^{liquid\ film}$ 7.7 (CH_3S), 8.2 (COC), and 9.5 μ (C=S).

Anal. Calcd for $C_9H_{16}OS_2$: mol wt, 204. Found: mol ion, 204.

trans-**2-Methylcyclohexyl-S-methyl Xanthate** (**6**).—1-Methyl 1-cyclohexene[39] (1.3 g) was hydroborated with oxidative work-up according to the *in situ* procedure of Sondheimer, *et al.*,[40] to produce, in *ca.* 70% yield, 2-methylcyclohexanol shown by gas chromatography (conditions A) to contain less than 2% of the *cis* isomer. This material was further purified by gas chromatography to yield *trans*-2-methylcyclohexanol (**46**) containing less than 1% of the *cis* compound. A portion (184 mg) of this material was converted into the S-methyl xanthate **6** according to procedure A. The crude xanthate was purified by gas chromatography (conditions B) to yield the mass spectral and analytical samples: $\lambda_{max}^{liquid\ film}$ 7.6, 8.2, and 9.5 μ.

Anal. Calcd for $C_9H_{16}OS_2$: C, 52.90; H, 7.89; mol wt, 204. Found: C, 52.73; H, 8.04; mol ion, 204 (by high resolution $C_9H_{16}OS_2$).

cis-**2-Methylcyclohexyl Acetate** (**7**).[41,42] **Procedure B.**—Alcohol **45** (330 mg, 2.9 mmol) was dissolved in 1.5 ml of reagent quality chloroform and 0.4 g (5.1 mmol) of reagent pyridine was added. The solution was cooled to 0° with stirring and *ca* a 1.2-fold *M* excess (3.5 mmol) of acetyl chloride added dropwise. The reaction flask was then stoppered and allowed to warm to 25° with continued stirring. After 12 hr, the mixture was poured into cold water, extracted with ether, washed twice with 10% hydrochloric acid, twice with 5% sodium hydroxide solution and twice with cold water, and dried for 4 hr over anhydrous magnesium sulfate. The ether was evaporated under reduced pressure (20°, 35 mm) and the crude ester purified by hot-box distillation (100–120°, 35 mm) and subsequent gas chromatography on a 15% Apiezon L column (10 ft × 0.25 in.) at 175° (conditions D): $\lambda_{max}^{liquid\ film}$ 5.7 (C=O), 7.3 (CH_3OC–), and 8.0 μ (COC).

Anal. Calcd for $C_9H_{16}O_2$: mol wt, 156. Found: mol ion, 156.

trans-**2-Methylcyclohexyl Acetate** (**8**).[41,42]—Alcohol **46** on a 20-mg scale yielded by a method identical with procedure B 15 mg of the desired *trans* acetate: $\lambda_{max}^{liquid\ film}$ 5.7, 7.3, and 8.0 μ.

Anal. Calcd for $C_9H_{16}O_2$: mol wt, 156. Found: mol ion, 156.

trans-**2-Methylcyclohexyl propionate** (**23**),[42] **butyrate** (**24**),[42] **valerate** (**25**),[42] **and octanoate** (**26**)[42] were all synthesized from alcohol **46** on a 20-mg scale by a method identical with procedure B, but employing the appropriate higher homolog in place of acetyl chloride. All were purified by gas chromatography employing conditions D, except for octanoate **26** for which column temperature was 200°: propionate, $\lambda_{max}^{liquid\ film}$ 5.7, 7.3, 7.4, and 8.4 μ (*Anal.* Calcd for $C_{10}H_{18}O_2$: mol wt, 170. Found: mol ion, 170); butyrate, $\lambda_{max}^{liquid\ film}$ 5.7, 7.3, 7.4, and 8.4 μ (*Anal.* Calcd for $C_{11}H_{20}O_2$: mol wt, 184. Found: mol ion, 184); valerate, $\lambda_{max}^{liquid\ film}$ 5.7, 7.2, 8.0, and 8.5 μ (*Anal.* Calcd for $C_{12}H_{22}O_2$: mol wt, 198. Found: mol ion, 198); octanoate, $\lambda_{max}^{liquid\ film}$ 5.7, 7.2, 8.0, and 8.5 μ (*Anal.* Calcd for $C_{15}H_{28}O_2$: mol wt, 240. Found: mol ion, 240, (wk).

1-d_1-2-Methylcyclohexyl Esters and S-Methyl Xanthates.—1-d_1-2-Methylcyclohexanol was prepared by the reduction[43] of 2-methylcyclohexanone[44] in dry ethereal solution with lithium aluminum deuteride.[45] The resulting alcoholic mixture (30% *cis*, 70% *trans*) was purified by preparative gas chromatography (conditions A) to give the pure (>99%) *cis*- (**47**) and *trans*- (**48**) 1-d_1-alcohols which were converted into the following requisite derivatives according to procedures A and B: *trans*-**1-d_1-2-methylcyclohexyl-S-methyl xanthate** (**10**), $\lambda_{max}^{liquid\ film}$ 7.6, 8.2, and 9.4 μ (*Anal.* Calcd for $C_9H_{15}OS_2D$: mol wt, 205. Found: mol ion, 205); *cis*-**1-d_1-2-methylcyclohexyl-S-methyl xanthate** (**15**) (*Anal.* Calcd for $C_9H_{15}OS_2D$: mol wt, 205. Found: mol ion, 205); *trans*-**1-d_1-2-methylcyclohexyl acetate** (**27**) (*Anal.* Calcd for $C_9H_{15}O_2D$: mol wt, 157. Found: mol ion, 157); *cis*-**1-d_1-2-methylcyclohexyl acetate** (**33**) (*Anal.* Calcd for $C_9H_{15}O_2D$: mol wt, 157. Found: mol ion, 157); *trans*-**1-d_1-2-methylcyclohexyl valerate** (**38**) (*Anal.* Calcd for $C_{12}H_{21}O_2D$: mol wt, 199. Found: mol ion, 199).

trans-**2-d_1-2-Methylcyclohexyl Esters and S-Methyl Xanthate.**—2-d_1-2-Methylcyclohexanol was prepared by the *in situ* deuterohydroboration of 1-methyl-1-cyclohexene following the general procedure of Sondheimer, *et al.*,[40] employing, however, lithium aluminum deuteride[45] instead of lithium aluminum hydride. The resulting alcoholic material (98% *trans*) was subjected to preparative gas chromatography (conditions A) and the resulting product (>99% *trans*) was employed both for the preparation of the required derivatives according to procedures A and B and for the subsequent preparation of *cis*-2-d_1-2-methylcyclohexanol. This purified *trans*-2-d_1-alcohol (**49**) exhibited in its nmr spectrum a sharp singlet at δ 1.00 ppm, whereas in the unlabeled *trans*-2-methylcyclohexanol this signal appears as a highly distorted doublet (J = 4 cps) centered *ca.* 1.02 ppm. The S-methyl xanthates exhibited the following properties: *trans*-**2-d_1-2-methylcyclohexyl-S-methyl xanthate** (**11**), $\lambda_{max}^{liquid\ film}$ 4.7 (CD), 7.6, 8.2, and 9.4 μ (*Anal.* Calcd for $C_9H_{15}OS_2D$: mol wt, 205. Found: mol ion, 205); *trans*-**2-d_1-2-methylcyclohexyl acetate** (**28**); $\lambda_{max}^{liquid\ film}$ 4.7 (CD), 5.8 (C=O), 7.3, and 8.1 μ (*Anal.* Calcd for $C_9H_{15}O_2D$: mol wt, 157. Found: mol ion, 157); *trans*-**2-d_1-2-methylcyclohexyl valerate** (**39**), $\lambda_{max}^{liquid\ film}$ 4.7, 5.8, 7.3, 7.5, 8.0, and 8.5 μ (*Anal.* Calcd for $C_{12}H_{21}O_2D$: mol wt, 199. Found: mol ion, 199).

cis-**2-d_1-2-Methylcyclohexanol** (**50**). **Procedure C.**—Greater than 99% *trans*-2-d_1-2-methylcyclohexanol (**49**, 1.4 g, 2% d_0 and 98% d_1 by calculation from the low-resolution mass spectrum of S-methyl xanthate **11**) was oxidized under Jones conditions[46,47] to yield 2-d_1-2-methylcyclohexanone. This material was then reduced with lithium aluminum hydride in dry ether to yield a crude alcoholic mixture (0.9 g, 30% *cis*, 70% *trans*) which was separated by gas chromatographic conditions A to yield the pure *cis* isomer (**50**). This carbinol was subsequently converted into the required xanthate and acetate by application of procedures A and B. The S-methyl xanthates exhibited the following properties: *cis*-**2-d_1-2-methylcyclohexyl-S-methyl xanthate** (**16**), $\lambda_{max}^{liquid\ film}$ 4.7, 7.6, 8.2, 9.4, and 9.5 μ (*Anal.* Calcd for $C_9H_{15}OS_2D$: mol wt, 205. Found: mol ion, 205); *cis*-**2-d_1-2-methylcyclohexyl acetate** (**34**), $\lambda_{max}^{liquid\ film}$ 4.7, 5.7, and 8.1 μ (*Anal.* Calcd for $C_9H_{15}O_2D$: mol wt, 157. Found: mol ion, 157).

trans-**Methyl-d_3-2-methylcyclohexyl Acetate** (**37**) **and S-Methyl Xanthate** (**13**).—Methyl-d_3-1-methylcyclohexene,[48] pre-

(37) W. Hückel and A. Hubele, *Ann.*, **613**, 36 (1958).

(38) C. Djerassi, I. T. Harrison, O. Zagneetko, and A. L. Nussbaum, *J. Org. Chem.*, **27**, 1173 (1962).

(39) Purchased from Aldrich Chemical Co., Inc., Milwaukee, Wis., and freed of a small amount of contaminating 3- and/or 4-methyl isomers by preparative gas chromatography on a 15% Apiezon L column (10 ft × 0.25 in.) at 100° (conditions C).

(40) M. Nussim, Y. Mazur, and F. Sondheimer, *ibid.*, **29**, 1120 (1964).

(41) See also (a) G. A. C. Gough, H. Hunter, and J. Kenyon, *J. Chem. Soc.*, 2065 (1926); (b) W. Hückel and K. Hagenguth, *Chem. Ber.*, **64**, 2892, 2894 (1931); (c) R. T. Arnold, G. G. Smith, and R. M. Dodson, *J. Org. Chem.*, **15**, 1256 (1950); (d) W. J. Bailey and L. Nicholas, *ibid.*, **21**, 854 (1956).

(42) (a) M. Murat, *Ann. Chim. Phys.*, **16**, 108 (1909); (b) J. B. Senderens and J. Aboulenc, *Ann. Chim.*, **18**, 176 (1922).

(43) *Cf.* D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.*, **72**, 5743 (1950).

(44) Purchased from Eastman Organic Chemicals, Distillation Products Industries, Rochester, N. Y.

(45) Lithium aluminum deuteride (>99.5%) was purchased from Ventron Corp., Metal Hydrides Division, Beverley, Mass.

(46) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(47) Jones oxidation, even though some acid is present, does not cause significant back exchange at the enolizable α positions during the normal oxidation period (10 min). See, also, J. Fishman, *J. Amer. Chem. Soc.*, **87**, 3456 (1965).

(48) We thank Dr. Peter Brown of this laboratory for a sample of this material. See, also, R. A. Cotton, J. H. Fassnacht, W. D. Horrocks, Jr., and N. A. Nelson, *J. Chem. Soc.*, 4138 (1959).

pared by sequential addition of d_3-methylmagnesium iodide[49] to cyclohexanone,[44] xanthation,[50] and pyrolysis, was hydroborated by the *in situ* method of Sondheimer, *et al.*,[40] and gave, after oxidative work-up, an alcoholic mixture containing 80% of the desired *trans*-methyl-d_3-2-methylcyclohexanol. This material was purified by gas chromatography (conditions A) to give *trans* alcohol (>99%) (**51**) which was then treated according to procedures A and B to yield the required derivatives: ***trans*-methyl-d_3-2-methylcyclohexyl-S-methyl xanthate** (**13**), $\lambda_{max}^{liquid\ film}$ 4.5, 7.6, 8.2, and 9.5 μ (*Anal.* Calcd for $C_9H_{13}OS_2D_3$: mol wt, 207. Found: mol ion, 207); ***trans*-methyl-d_3-2-methylcyclohexyl acetate** (**32**), $\lambda_{max}^{liquid\ film}$ 4.5, 5.7 (C=O), 7.3, and 8.1 μ (*Anal.* Calcd for $C_9H_{13}O_2D_3$: mol wt, 159. Found: mol ion, 159).

2,6,6-d_3-2-Methylcyclohexyl Esters and S-Methyl Xanthates.—2-Methylcyclohexanone was exchanged three times with 10% deuteriohydrochloric acid–deuteriophosphoric acid solution according to the procedure of Seibl and Gäumann.[51] This exchanged ketone (**52**) was reduced with lithium tri-*t*-butoxyaluminchydride in dry tetrahydrofuran solution according to the procedure of Brown[52] to give an alcoholic mixture containing 60% of the *trans* and 40% of the *cis* isomer. These components were separated by preparative gas chromatography (conditions A) and converted by application of procedures A and B into the xanthates and esters: ***trans*-2,6,6-d_3-2-methylcyclohexyl-S-methyl xanthate** (**12**), $\lambda_{max}^{liquid\ film}$ 4.5, 4.7, 7.6, 8.1, 9.3, and 9.4 μ (*Anal.* Calcd for $C_9H_{13}OS_2D_3$: mol wt, 207. Found: mol ion, 207); ***trans*-2,6,6-d_3-2-methylcyclohexyl acetate** (**31**), $\lambda_{max}^{liquid\ film}$ 4.6, 4.7, 5.8, 7.3, and 8.1 μ (*Anal.* Calcd for $C_9H_{13}O_2D_3$: mol wt, 159. Found: mol ion, 159); ***trans*-2,6,6-d_3-2-methylcyclohexyl valerate** (**41**), $\lambda_{max}^{liquid\ film}$ 4.5, 4.7, 5.7, 7.3, 8.0, and 8.5 μ (*Anal.* Calcd for $C_{12}H_{19}O_2D_3$: mol wt, 201. Found: mol ion, 201); ***cis*-2,6,6-d_3-2-methylcyclohexyl-S-methyl xanthate** (**19**) (*Anal.* Calcd for $C_9H_{13}OS_2D_3$: mol wt, 207. Found: mol ion, 207); ***cis*-2,6,6-d_3-2-methylcyclohexyl acetate** (**37**), $\lambda_{max}^{liquid\ film}$ 4.7, 5.7, 7.3, and 8.0 μ (*Anal.* Calcd for $C_9H_{13}O_2D_3$: mol wt, 159. Found: mol ion, 159).

***trans*-2-Methylcyclohexyl-S-methyl-d_3 Xanthate** (**14**).—*trans*-2-Methylcyclohexanol (**46**) was converted on a 30-mg scale into the S-methyl xanthate by the use of procedure A. However, instead of methyl iodide in the final step, d_3-methyl iodide[49] was employed: $\lambda_{max}^{liquid\ film}$ 8.1, 9.4, and 9.9 μ (SCD_3).

Anal. Calcd for $C_9H_{13}OS_2D_3$: mol wt, 207. Found: mol ion, 207.

3,3-d_2-1-Methyl-1-cyclohexene.—2,6,6-d_3-Methylcyclohexanone (**52**) was reduced in dry ethereal solution with a fourfold excess of lithium aluminum hydride[43] and the crude alcoholic mixture (30% *cis*, 70% *trans*) converted directly without further purification into the S-methyl xanthate by the procedure of Djerassi, *et al.*[38]

The crude xanthate thus obtained (containing a large amount of dimethyl trithiocarbonate,[53] as an impurity) was pyrolyzed over powdered soft glass in a flask equipped with a Vigreux column and a nitrogen inlet tube by heating in a Wood's metal bath at 200–210°. The pyrolysate was collected in a Dry Ice–isopropyl alcohol cooled trap. After the pyrolysis was complete (0.5 hr), the trap was removed and warmed slowly to ambient temperature allowing the slow ebullition of most of the methyl mercaptan and carbonyl sulfide which were collected in addition to the desired olefins. The olefinic fraction (*ca.* 50% 1-methyl-1-cyclohexene and 50% 3-methyl-1-cyclohexene[54] by comparative gas chromatography) was purified by gas chromatography (conditions D) to yield the 1-methyl-1-cyclohexene fraction containing less than 1% of the isomeric olefin.

This material was examined by infrared, nmr, and mass spectral measurements. The low-resolution mass spectrum of this material cn comparison with that of the unlabeled compound gave the isotopic content 94% d_2 and 6% d_3.[55] The infrared spectrum showed $\lambda_{max}^{liquid\ film}$ 4.6 (CD), 4.8 (CD), and 6.0 μ (C=C, wk). The nmr spectrum of the labeled compound showed the same three main structural features as did that of the unlabeled olefin: broadened signals centered at δ 5.4 ppm (1 H) (C=CH), 1.92 ppm (4 H) (C=CH–), and that for the remaining seven hydrogens at δ 1.63 ppm (CH_3C=C and $-CH_2-$); however, in the d_2 compound, the signal originally at δ 1.92 ppm is now centered at 1.85 ppm and integrates to only two hydrogens, thus establishing the site of deuteration.

***trans*-6,6-d_2-2-Methylcyclohexanol and Derivatives.**—3,3-d_2-1-Methyl-1-cyclohexene (230 mg) was hydroborated according to the *in situ* conditions of Sondheimer, *et al.*,[40] and yielded, after oxidative work-up, a crude alcoholic mixture (*ca.* 150 mg) containing 90% of the desired *trans*-ol. This material was subjected to preparative gas chromatography (conditions A) to give *trans*-6,6-d_2-2-methylcyclohexanol (**53**) of greater than 99% purity: $\lambda_{max}^{liquid\ film}$ 2.9 (OH), 4.5, 4.7, 9–10 μ multiplet (CO). One portion of this deuterated alcohol was converted into the required derivatives (on a 10-mg scale) by procedures A and B, while a second portion was treated to yield the *cis* isomer. The derivatives and properties follow: ***trans*-6,6-d_2-2-methylcyclohexyl acetate** (**30**), $\lambda_{max}^{liquid\ film}$ 4.5, 4.7, 5.7, 7.3, and 8.1 μ (*Anal.* Calcd for $C_9H_{14}O_2D_2$: mol wt, 158. Found: mol ion, 158); ***trans*-6,6-d_2-2-methylcyclohexyl valerate** (**40**), $\lambda_{max}^{liquid\ film}$ 4.5, 4.7, 5.75, 7.3, and 8.5 μ (*Anal.* Calcd for $C_{12}H_{20}O_2D_2$: mol wt, 200. Found: mol ion, 200).

***cis*-6,6-d_2-2-Methylcyclohexanol and Derivatives.**—On a 100-mg scale, *trans*-6,6-d_2-methylcyclohexanol was oxidized by the Jones procedure[c6,47] and back reduced (procedure C) employing lithium tri-*t*-butoxyaluminohydride[52] in place of lithium aluminum hydride in the reduction step. The crude alcoholic mixture (40% of the desired *cis* isomer) was separated by preparative gas chromatography (conditions A) to yield the desired *cis*-6,6-d_2-2-methylcyclohexanol (20 mg) (**54**), containing less than 1% impurities. This material was then converted into the desired xanthate and acetate by application of procedures A and B: ***cis*-6,6-d_2-2-methylcyclohexyl-S-methyl xanthate** (**18**) (*Anal.* Calcd for $C_9H_{14}OS_2D_2$: mol wt, 206. Found: mol ion, 206); ***cis*-6,6-d_2-2-methylcyclohexyl acetate** (**36**) (*Anal.* Calcd for $C_9H_{14}O_2D_2$: mol wt, 158. Found: mol ion, 158).

4-d_1-4-Hydroxycyclohexanone Ethylene Ketal (**55**).—Cyclohexane-1,4-dione 4-monoethylene ketal (2.28 g), prepared according to the methods of Jones[56] and Plieninger[57] and containing less than 1% of 4-hydroxycyclohexanone ethylene ketal, was reduced in dry tetrahydrofuran solution with a slight excess of lithium aluminum deuteride.[43] The crude product [$\lambda_{max}^{liquid\ film}$ 2.9 (OH) and 4.7 μ (CD)] was used directly in the subsequent step.

4-d_1-4-Tosyloxycyclohexanone Ethylene Ketal (**56**).—Ketal **55** (2.4 g) was treated with *p*-toluenesulfonyl chloride in dry pyridine according to the procedure of Mićović and Stojiljković[58] to yield the crude ketal tosylate (4.0 g; mp 77–78°; $\lambda_{max}^{liquid\ film}$ 4.6 (CD), 5.2 and 6.3 (arom), 6.9 (SO_2), 7.4 (CO), 8.5 (SO_2), and 8.4–13.5 μ (ketal CO bands)). This material was used directly without purification in the ensuing displacement reaction.

Displacement Reaction on 4-d_1-4-Tosyloxycyclohexanone Ethylene Ketal.[47,59]—Tosylate **56** (3.9 g, 0.01 mmol) was dis-

(49) d_3-Methyl iodide (>99 % d_3) was purchased from Merck Sharpe and Dohme of Canada, Ltd., Montreal, Quebec.

(50) R. A. Benkeser and J. J. Hazdra, *J. Amer. Chem. Soc.*, **81**, 228 (1959).

(51) J. Seibl and T. Gäumann, *Helv. Chim. Acta*, **46**, 2857 (1963).

(52) H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.*, **78**, 252 (1956).

(53) This yellow, highly odiferous oil was present to a varying extent in all S-methyl xanthate preparations connected with this study and presumably arises through an alcoholate-initiated condensation process with excess carbon disulfide. Very little was formed in a blank experiment in which the alcohol was omitted. It was readily separable by gas chromatography (conditions B) and was identified in its infrared ($\lambda_{max}^{liquid\ film}$ 7.1 and 7.6 (CH_3S), 9.2 (C=S), 10.4, 11.4, 11.6, and 12.2 μ) and high resolution mass spectra [mol ion, 138 ($C_3H_6S_3^+$); base peak *m/e* 91 ($C_2H_3S_2^+$, M − 47)].

(54) Under gas chromatographic conditions D, 3-methyl-1-cyclohexene, 4-methyl-1-cyclohexene, and methylenecyclohexane had nearly equal retention times; hence this fraction may contain minor portions of the latter isomers, if they are formed under the pyrolytic conditions.

(55) The formation of d_3-1-methyl-1-cyclohexene in this pyrolytic process is most intriguing, since a deuterium rearrangement is required for the generation of this product. An analogous behavior was noted by Thomas and Willhalm[12] in the pyrolysis of an isomer mixture of 1,3,3-d_3-carvomenthyl acetate to yield as one of the products 3,3-d_2-menth-2-ene having the isotopic content 19.5% d_3, 71% d_2, and 9.5% d_1; however, no comment on this anomalous result was offered by these authors. The explanation offered by us[22] to explain the retention of deuterium label in the 1-methyl-1-cyclohexene fraction from pyrolysis of *cis*-2-d_1-2-methylcyclohexyl-S-methyl xanthate (**16**) should also apply here.

(56) E. R. H. Jones and F. Sondheimer, *J. Chem. Soc.*, 615 (1949).

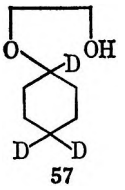
(57) H. Plieninger and H. J. Grasshoff, *Chem. Ber.*, **90**, 1973 (1957).

(58) V. M. Mićović and A. Stojiljković, *Tetrahedron*, **4**, 186 (1958).

(59) See (a) W. A. Sanderson and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 4185 (1966); (b) ref 46.

solved in 35 ml of sodium-dried ether and added slowly (under nitrogen and with the exclusion of moisture) to a stirred suspension of 849 mg (0.02 mmol) of lithium aluminum deuteride in 10 ml of dried ether. After the addition was complete (0.5 hr), the reaction was heated to reflux with continued stirring and this condition maintained for 14 hr. After this time, the white suspension was cooled and the mixture decomposed with saturated sodium sulfate solution followed by solid sodium sulfate. The crystalline complex was removed by suction filtration through a layer of Celite and washed well with dry ether, and the organic layers were stripped under reduced pressure (20°, 35 mm) using a rotary evaporator.

The crude oil (2.3 g) was hot-box distilled (80–140°, 35 mm) and then subjected to preparative gas chromatography on a 15% Apiezon L column (5 ft × 0.25 in.) at 130°. Three components were found to be present in the approximate ratio 2:1:4; the first two of these were virtually inseparable under these conditions and were collected as a single fraction (523 mg) for subsequent treatment. The major component (*ca.* 1.0 g) was shown to be 2-(1′,4′,4′-d_3-cyclohexyloxy)ethanol (**57**) by a combination of mass spectrometric, infrared spectral,



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and gas chromatographic comparison with authentic unlabeled material synthesized according to the procedure of Eliel:[60,61] $M^+ = m/e$ 147 (2% d_2, 98% d_3); $\lambda_{max}^{liquid\ film}$ 3.0 (OH), 4.6 and 4.8 (CD), and 8.7–10.0 μ (CO).

4,4-d_2-Cyclohexanone.[62]—The crude ketal fraction (523 mg) from the displacement reaction (containing 66% of the desired cyclohexanone ethylene ketal by gas chromatographic comparison with authentic material) was hydrolyzed according to the procedure or Magerlein and Levin[63] to give a ketonic mixture (d_2-cyclohexanone plus Δ^2- and Δ^3-cyclohexenones) which was separable by gas chromatography on a 20% Carbowax 20M column (10 ft × 0.25 in.) at 130° (conditions E). The cyclohexanone fraction was recycled until it contained less than 1% impurities: yield, 133 mg.

The d_3-ethylene glycol monether (**57**, 833 mg) was cleaved by the method of Johnson[64] to yield 1,4,4-d_3-cyclohexanol (400 mg) which was purified by gas chromatography on a 15% Apiezon L column (5 ft × 0.25 in.) at 110° (conditions E). This material was oxidized under Jones conditions[46] to yield the crude ketone (216 mg) which was purified by gas chromatography employing conditions E above: from both routes, $\lambda_{max}^{liquid\ film}$ 4.5 and 4.7 (CD) and 5.8 μ (C=O). *Anal.* Calcd for $C_6H_8OD_2$: mol wt, 100. Found: mol ion, 100 (97% d_2, 3% d_1).

4,4-d_2-2-Methylcyclohexanols and Derivatives.—4,4-d_2-Cyclohexanone (**61**, 216 mg) was methylated in dry toluene with sodium *t*-amylate and dimethyl sulfate according to the procedure of Seibl and Gäumann.[61] The products from this reaction [4,4-d_2-cyclohexanone (40%), 4,4-d_2-2-methylcyclohexanone (50%), and 4,4-d_2-2,2-dimethylcyclohexanone (10%)] were separated by gas chromatography on a 20% Apiezon L column (10 ft × 0.25 in.) at 120°. The resulting pure 4,4-d_2-2-methylcyclohexanone (**62**, *ca.* 50 mg; $\lambda_{max}^{liquid\ film}$ 4.6, 4.8, and 5.8 μ) was reduced with lithium aluminum hydride in dry ether to yield the crude alcoholic mixture (30% *cis*, 70% *trans*) which was in turn separated into the pure components (**63** and **64**) by gas chromatography (conditions A). Procedures A and B were applied to obtain the required xanthates and acetates on a 4–10-mg scale: ***trans*-4,4-d_2-2-methylcyclohexanol** (**63**), $\lambda_{max}^{liquid\ film}$ 3.0, 4.6, and 4.8 μ (*Anal.* Calcd for $C_7H_{12}OD_2$: mol wt, 116. Found: mol ion, 116); ***trans*-4,4-d_2-2-methylcyclohexyl acetate** (**29**), $\lambda_{max}^{liquid\ film}$ 4.6, 4.8, 7.3, and 8.1 μ (*Anal.* Calcd for $C_9H_{14}O_2D_2$: mol wt, 158. Found: mol ion, 158); ***cis*-4,4-d_2-2-Methylcyclohexanol** (**64**), $\lambda_{max}^{liquid\ film}$ 2.9, 4.6, and 4.8 μ (*Anal.* Calcd for $C_7H_{12}OD_2$: mol wt, 116. Found: mol ion, 116); ***cis*-4,4-d_2-2-methylcyclohexyl-S-methyl xanthate** (**17**) (*Anal.* Calcd for $C_9H_{14}OS_2D_2$: mol wt, 206. Found: mol ion, 206); ***cis*-4,4-d_2-2-methylcyclohexyl acetate** (**35**), $\lambda_{max}^{liquid\ film}$ 2.6, 2.8, 5.8, 7.3, and 8.0 μ (*Anal.* Calcd for $C_9H_{14}O_2D_2$: mol wt, 158. Found: mol ion, 158).

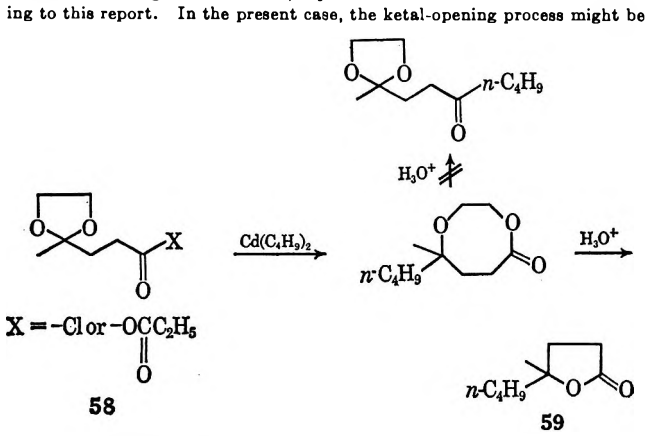
1,2,2,6,6-d_5-Cyclohexyl Acetate (**22**) **and S-Methyl Xanthate** (**65**).—Cyclohexanone was exchanged three times with 10% deuteriohydrochloric acid–deuteriophosphoric acid according to the procedure of Seibl and Gäumann,[61] then reduced with lithium aluminum deuteride in dry ether to yield the crude alcohol. This material was purified by preparative gas chromatography (conditions E) and converted by procedures A and B into the two requisite derivatives: **1,2,2,6,6-d_5-cyclohexyl-S-methyl xanthate** (**65**) [*Anal.* Calcd for $C_8H_9OS_2D_5$: mol wt, 195. Found: mol ion, 195 (1% d_1, 3% d_2, 5% d_3, 8% d_4, 83% d_5)]; **1,2,2,6,6-d_5-cyclohexyl acetate** (**22**), $\lambda_{max}^{liquid\ film}$ 4.5, 4.7, 5.7, 7.3, and 7.9 μ (*Anal.* Calcd for $C_8H_9O_2D_5$: mol wt, 147. Found: mol ion, 147).

Registry No.—**5**, 15288-12-7; **6**, 15288-13-8; **7**, 15288-14-9; **8**, 15288-15-0; **10**, 15288-16-1; **11**, 15288-17-2; **12**, 15288-18-3; **13**, 15288-19-4; **14**, 15288-20-7; **15**, 15288-21-8; **16**, 15288-22-9; **17**, 15288-23-0; **18**, 15288-24-1; **19**, 15288-25-2; 1,4,4-d_3-cyclohexanol, 15288-26-3; 3,3-d_2-1-methyl-1-cyclohexene, 15288-03-6; **22**, 15287-78-2; **23**, 15287-79-3; **24**, 15287-80-6; **25**, 15287-81-7; **26**, 15287-82-8; **27**, 15287-83-9; **28**, 15285-91-3; **29**, 15285-92-4; **30**, 15285-93-5; **31**, 15285-94-6; **32**, 15285-95-7; **33**, 15285-96-8; **34**, 15285-97-9; **35**, 15285-98-0; **36**, 15285-99-1; **37**, 15286-00-7; **38**, 15286-01-8; **39**, 15286-0-29; **40**, 15285-93-5; **41**, 15286-04-1; **53**, 15286-05-2; **55**, 15313-92-5; **56**, 15286-06-3; **63**, 15286-07-4; **64**, 15286-08-5.

Acknowledgment.—We wish to thank Professor J. I. Brauman for helpful discussions during the preparation of this manuscript.

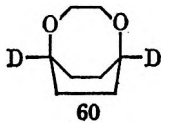
(60) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Amer. Chem. Soc.*, **84**, 2371 (1962).

(61) A similar 1,4 participation has recently been reported by R. A. LeMahieu (Abstracts of Papers, 153rd Meeting of the American Chemical Society, Miami Beach, Fla., April 1967, p 0-24), who noted that in the attempted conversion of ketal acid chloride or mixed anhydride of type **58** to the butyl ketone with di-*n*-butylcadmium, the only product isolated on acid work-up was the five-membered lactone (**59**). Evidence for the intermediacy of the eight-membered 1,4-cyclic diether has been obtained according to this report. In the present case, the ketal-opening process might be



58 **59**

envisioned as proceeding through the analogous eight-membered cyclic intermediate (**60**) which is then attacked by deuteride at one of the bridge-



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head positions yielding the ethylene glycol monoether (**57**); however, this hypothesis has not yet been confirmed.

(62) 4,4-d_2-Cyclohexanone has previously been synthesized by other routes: *cf.* (a) ref 51; (b) J. B. Lambert, *J. Amer. Chem. Soc.*, **89**, 1836 (1967). However, the present synthesis gives the best isotopic content in the final product of any reported to date.

(63) B. J. Magerlein and R. H. Levin, *ibid.*, **77**, 1904 (1955).

(64) W. S. Johnson and R. B. Kinnel, *ibid.*, **88**, 3861 (1966). We wish to express our sincerest appreciation to Dr. Arne van der Gen of Professor Johnson's laboratory for informing us of his recent improvements on the method.

The Pyrolysis of the Epimeric d_0- and 2-d_1-2-Methylcyclohexyl-S-methyl Xanthates and Acetates[1,2]

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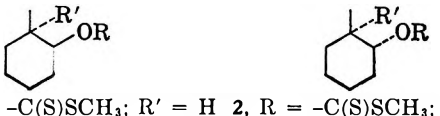
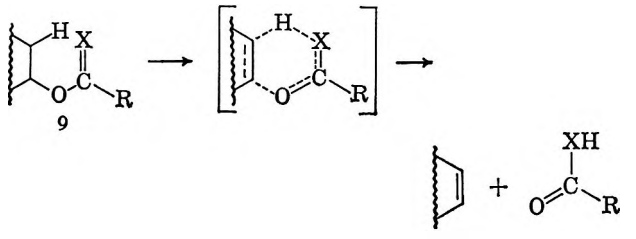
The Chugaev xanthate and ester pyrolysis reactions have been examined in the epimeric *cis*- and *trans*-2-methylcyclohexyl-S-methyl xanthates and acetates by comparison of results obtained for the unlabeled and 2-d_1-labeled substrates. While the olefinic products obtained from the pyrolysis of the *trans*-2-d_1 xanthate (**6**) and acetate (**8**) exhibit isotopic contents consistent with those to be expected through operation of a homogeneous *cis*-cyclic elimination process, the products from the *cis*-2-d_1 xanthate (**5**) and acetate (**7**) do not. In the latter compounds, kinetic deuterium isotope effects (k_D/k_H) have been calculated (1.0 in **5** and 0.67 in **7**) and from these values and isotopic content data for the 1-methyl-1-cyclohexene fraction (44% d_1 in **5** and 78% d_1 in **7**) possible ionic mechanisms have been proposed for the net *trans*-elimination process in these compounds.

In the course of our investigation[3] of the electron impact induced elimination of the elements of xanthic and acetic acid from the epimeric 2-methylcyclohexyl-S-methyl xanthates (**1** and **2**) and acetates (**3** and **4**), we had cause to examine closely the pyrolysis of the unlabeled compounds and their 2-d_1-labeled analogs (**5**–**8**). The present paper records these results, which offer an interesting comparison between thermolytic and electron impact promoted phenomena.



1, R = -C(S)SCH$_3$; R′ = H **2**, R = -C(S)SCH$_3$; R′ = H
3, R = -C(O)CH$_3$; R′ = H **4**, R = -C(O)CH$_3$; R′ = H
5, R = -C(S)SCH$_3$; R′ = D **6**, R = -C(S)SCH$_3$; R′ = D
7, R = -C(O)CH$_3$, R′ = D **8**, R = -C(O)CH$_3$; R′ = D

The pyrolytic elimination reaction in esters[4] and xanthates[4,5] (the Chugaev reaction) is known to result in the nearly exclusive abstraction of a *cis*-β-hydrogen atom and such elimination processes have found widespread synthetic utility as a result of this striking selectivity in the conversion of alcohols to olefins. These eliminations have been visualized as proceeding[4] by a highly concerted mode such as **9** → **10** + **11**, in which, in the activated complex, little charge separation develops and some double-bond character exists between the incipient olefinic carbon atoms. This view has been supported by the observed substituent and isotope effects.[4] In the case of esters (R = alkyl), the acid fragment **11** is stable, while that produced in the pyrolysis of xanthates (the unknown xanthic acid) undergoes subsequent decomposition to carbonyl sulfide and mercaptan (RSH).

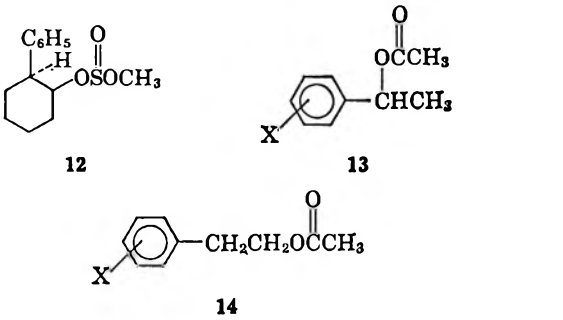


9 **10** **11**

X = O; R = -CH$_3$
or X = S; R = -SCH$_3$

While a concerted, *cis*-cyclic mechanism of the above type adequately explains the formation of the major portion of products in most pyrolytic elimination processes, minor quantities of net *trans* elimination do occur.[4,5] Such products are readily detected in cyclic systems where free rotation about carbon–carbon single bonds is precluded and it has been proposed that these products of net *trans* elimination may arise through the operation of radical[4] or ionic[6-8] mechanisms.

Esters[9,10] and S-methyl xanthates[8] of the bicyclic alcohol borneol (**15**) give, upon pyrolysis, products which can be best explained by invoking ionic intermediates[9,10] which may undergo subsequent Wagner–Meerwein rearrangement before suffering hydrogen loss. Thus, bornyl-S-methyl xanthate (**16**) yields[8] upon pyrolysis in the liquid state not only the expected bornylene (**17**), but also significant quantities of camphene (**18**) (30% optical purity) and tricyclene



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(1) We are indebted to the National Institutes of Health for financial support (Grant No. GM-06840). The purchase of the Atlas CH-4 mass spectrometer was made possible by NASA Grant No. NsG 81-60.

(2) Taken in part from the Ph.D. dissertation submitted by W. S. B. to the Graduate School, Stanford University, 1967.

(3) W. S. Briggs and C. Djerassi, *J. Org. Chem.*, **33**, 1612 (1968).

(4) C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960), and references therein.

(5) H. R. Nace, *Org. Reactions*, **12**, 57 (1962), and references therein.

(6) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, pp 500–507.

(7) Such ionic intermediates have been proposed by G. Berti [*J. Amer. Chem. Soc.*, **76**, 1217 (1954)] to explain the large amount (70–78%) of *trans* elimination which occurs in the liquid phase pyrolysis of *cis*-methyl (2-phenylcyclohexyl) sulfite (**12**) and by Smith and co-workers [R. Taylor, G. G. Smith, and W. Wetzel, *ibid.*, **84**, 4817 (1962)] to account for the excellent correlation obtained between k_{rel} for the pyrolysis (600°K) of substituted phenylethyl acetates of types **13** and **14** with Hammett σ^+ values.

(8) (a) A. Maccoll, "Kekulé Symposium," Butterworth and Co. Ltd., London, 1959, pp 230–249; (b) for a recent review of such processes, see A. Maccoll, *Advan. Phys. Org. Chem.*, **3**, 91 (1965).

(9) C. A. Bunton, K. Khaleeluddin, and D. Whittaker, *Nature*, **190**, 715 (1961).

(10) T. Sato, K. Murata, A. Nishimura, T. Tsuchiya, and N. Wasada, *Tetrahedron* **23** 1791 (1967).

(19). The low optical purity of the isolated camphene suggested[9] that stepwise decomposition through a carbonium ion intermediate was operative. (See Scheme I.)

Analogous "quasi-heterolytic processes"[8] yielding ionic intermediates have been proposed[6,8,11] for the pyrolysis of alkyl halides; however, the observation of significant isotope effects in certain cases has lead to some question[4] regarding these mechanisms.

Results

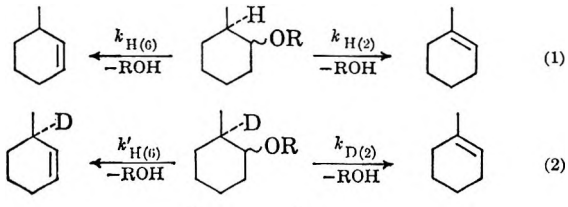
Xanthates **1** and **2** and their 2-d_1-labeled analogs (**5** and **6**) were pyrolyzed at 250° as described in the Experimental Section. In a like manner, acetates **3** and **4** and their deuterated counterparts (**7** and **8**) were pyrolyzed at 400°. In Table I are summarized the percentages of the various olefinic products,[12] as determined by analytical vapor phase chromatography and the isotopic content of these products as determined by mass spectrometry.

From the pyrolytic data in Table I, values of the kinetic deuterium isotope effect (k_D/k_H) for the elimination process in xanthates **1** and **2** may be calculated.[13] The values of 0.59–0.72 found for the *trans* xanthate (**2**) are in fairly good agreement with values of 0.50–0.59 previously reported[4,13] for ester pyrolyses. The *cis* xanthate (**1**), by contrast, exhibits no significant isotope effect. Inspection of the isotopic content of the olefins produced in the pyrolysis of the deuterated xanthates (**5** and **6**) (Table I) provides additional insight into the cause of this anomalous behavior.

(11) A. Maccoll and E. S. Swinbourne, *Proc. Chem. Soc.*, 409 (1960).

(12) Treatment of control mixtures of each of the isomeric methylcyclohexenes under the pyrolysis and work-up conditions both neat and in the presence of equimolar quantities of glacial acetic acid or methyl mercaptan failed to produce any significant isomerization as detected by subsequent vapor phase chromatography.

(13) These values were calculated by a method analogous to that of DePuy and co-workers [C. H. DePuy, R. W. King, and D. H. Froemsdorf, *Tetrahedron*, **7**, 123 (1959)]. By consideration of the kinetic processes (1 and 2) for the unlabeled and deuterium-labeled substrates, expressions 3 and 4 may be written relating the ratios of percentages of the two olefinic products at any time t to the ratio of the rate constants for the two decomposition pathways, assuming that both elimination processes are of the same molecular order (and presumably both unimolecular in such pyrolysis processes).



(1)

(2)

$$R = -\overset{O}{\overset{\|}{C}}CH_3 \text{ or } -\overset{S}{\overset{\|}{C}}SCH_3$$

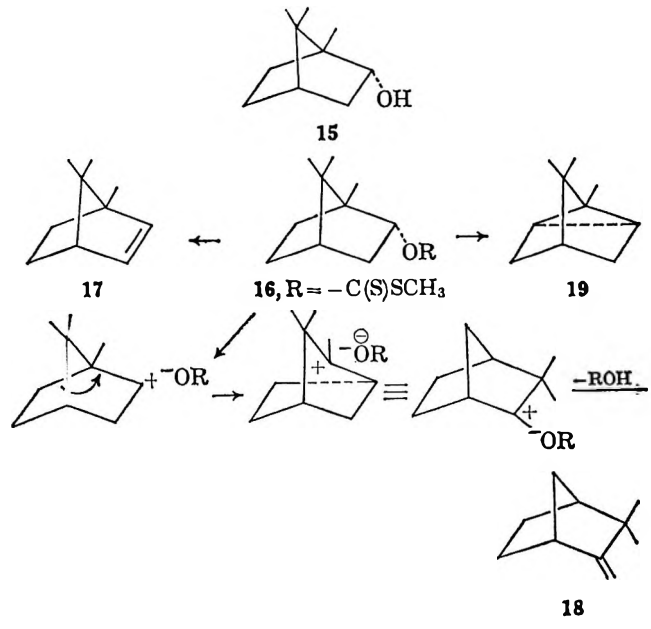
$$\frac{(\%\ H(2)\ \text{loss})_{d_0}}{(\%\ H(6)\ \text{loss})_{d_0}} = \frac{(\%\ \Delta^1\text{-})_{d_0}}{(\%\ \Delta^3\text{-})_{d_0}} = \frac{k_{H(2)}}{k_{H(6)}} \quad (3)$$

$$\frac{(\%\ D(2)\ \text{loss})_{2\text{-}d_1}}{(\%\ H(6)\ \text{loss})_{2\text{-}d_1}} = \frac{(\%\ \Delta^1\text{-})_{2\text{-}d_1}}{(\%\ \Delta^3\text{-})_{2\text{-}d_1}} = \frac{k_{D(2)}}{k'_{H(6)}} \quad (4)$$

By making the reasonable assumption that the rates of hydrogen loss from C-6 in the d_0 and 2-d_1 compounds are equal (*i.e.*, $k_{H(6)} \equiv k'_{H(6)}$), relations 3 and 4 may be combined to yield an expression (5) defining the kinetic deuterium isotope effect (k_D/k_H) for replacement of the C-2 hydrogen by deuterium in terms of the percentage composition of the olefinic mixture in the unlabeled and deuterium-labeled materials.

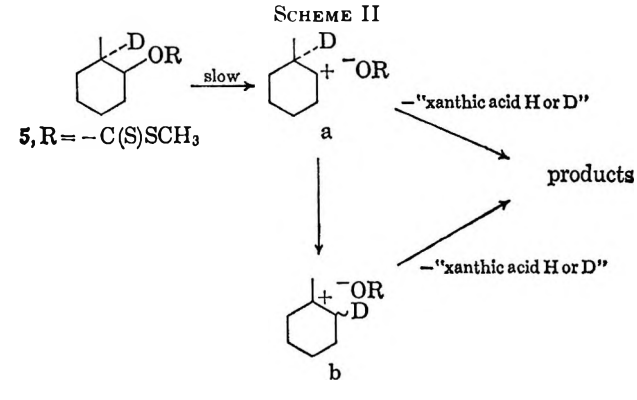
$$\frac{k_D}{k_H} = \frac{k_{D(2)}}{k_{H(2)}} = \frac{(\%\ \Delta^3\text{-})_{d_0} \times (\%\ \Delta^1\text{-})_{2\text{-}d_1}}{(\%\ \Delta^1\text{-})_{d_0} \times (\%\ \Delta^3\text{-})_{2\text{-}d_1}} \quad (5)$$

SCHEME I



While the olefins produced from the *trans* xanthate (**6**) show the expected isotopic contents for operation of a concerted, *cis*-cyclic elimination process, namely, nearly complete retention of deuterium label in the 1-methyl-1-cyclohexene and nearly complete loss of label in the formation of 1-methyl-1-cyclohexene, the results for the *cis* xanthate (**5**) are clearly not in accord with predictions. The retention of deuterium label in 44% of the 1-methyl-1-cyclohexene in this latter pyrolysis could be explained, however, by the postulation of a carbonium ion[6] intermediate of type a in one of the decomposition pathways of this isomer. This species (a) may either lose a proton or deuteron directly or undergo a 1,2-deuteride shift to yield the more stable tertiary carbonium ion (b) which subsequently loses a proton or deuteron to yield the olefinic products. In the activated complex leading to the elimination of the tertiary hydrogen in xanthate **5**, C–O bond breaking would be the dominant process, thus accounting for the lack of any observable kinetic deuterium isotope effect with this substrate. (See Scheme II.)

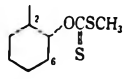
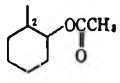
SCHEME II



However, it should be pointed out that, since these pyrolytic studies were carried out in a hot vpc column, their degree of homogeneity is not precisely known. While a path of type **5** → a → b → products may be operating, one cannot say with certainty whether it is

TABLE I

SUMMARY OF PYROLYTIC STUDIES ON 2-METHYLCYCLOHEXYL-S-METHYL XANTHATES AND ACETATES

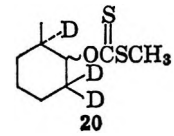
Compound	Pyrolysis conditions[a]	Percentage of olefin mixture[b]		k_D/k_H
				
trans-d_0 (2)	*c*	68	32	...
	d	65	35	...
	e	64	36	...
	f	66	34	...
	g	62	38	...
cis-d_0 (1)	*d*	29	71	...
	f	20	80	...
	g	10	90	...
trans-2-d_1 (6) {2% d_0 / 98% d_1}	*d*	54 (98% d_0)	46 (97% d_1)	0.62
	f	54	46	0.59
	g	54	46	0.72
cis-2-d_1 (5) {18% d_0 / 82% d_1}	*d*	28 {56% d_0 / 44% d_1}	72 {11% d_0 / 89% d_1}	1.0
	f	20	80	1.0
	g	10	90	1.0
2,6,6-d_3 (20) (97% d_2)	*d*	60	40	...
	e	50	50	...
	f	61	39	...
				
trans-d_0 (4)	*h*	56	44	...
	g	56	44	...
cis-d_0 (3)	*h*	9	91	...
	g	6	94	...
	i	58	42	...
trans-2-d_1 (8) {16% d_0 / 84% d_1}	*h*	41 (97% d_0)	59 (100% d_1)	0.56
	g	40	60	0.53
cis-2-d_1 (7) {18% d_0 / 82% d_1}	*h*	6 {22% d_0 / 78% d_1}	94 (100% d_1)	0.67
	g	4	96	0.67
	i	50	50	0.72

[a] See Experimental Section. [b] These values are corrected for the contribution of any significant quantities of the isomeric materials or isotopic contaminants and are considered reproducible to ±1%. [c] Unseasoned stainless steel, 250°. [d] Seasoned stainless steel, 250°. [e] Liquid phase, over powdered soft glass, 200°. [f] Pyrex tube, 250°. [g] Pyrex tube, 400°. [h] Seasoned stainless steel, 400°. [i] Seasoned stainless steel tube with a deposit of carbonaceous material from *ca.* 70 pyrolyses, 400°.

occurring as a true vapor phase reaction or on the walls of the hot tube as a surface-catalyzed process. In fact suggestive of at least partial intervention of such surface catalyzed processes is the observed sensitivity (Table I) of the product composition to the nature of the tube wall (seasoned stainless steel or Pyrex glass), to the presence of acidic carbonaceous residues, and to higher reaction temperature.[6] The observed temperature dependence of the anomalous 1-methyl-1-cyclohexene product in the total product mixture is, however, not that expected for total operation of a high-energy "quasi-heterolytic" process, since higher reaction temperature should result in an increase in the anomalus product rather than a decrease as noted in Table I.

The formation of a significant quantity (11%, Table I) of 3-methyl-1-cyclohexene in which all the deuterium label is lost is not easily accommodated by either the normal *cis*-cyclic elimination process or a "quasi-heterolytic" process of type **5** → a → products. and virtually demands the intervention of a surface catalyzed variant.

That this rearrangement of type **5** → b → products is not unique to the pyrolysis under conditions where surface catalysis might come into play is shown however by the pyrolysis of a mixture of 2,6,6-d_3-2-methylcyclohexyl-S-methyl xanthates (**20**) containing *cis*



20

(30%) and *trans* (70%) isomers in the liquid state (see Experimental Section). The olefins isolated from this pyrolysis [3-methyl-1-cyclohexene (50%) and 1-methyl-1-cyclohexene (50%)] also gave anomalous isotopic contents. While the 3-methyl-1-cyclohexene fraction was 100% d_2, the 1-methyl-1-cyclohexene produced had isotopic content 94% d_2 and 6% d_3.

The alternative radical process involving homolytic fission of the C–O bond would require a 1,2-hydrogen atom shift and would therefore not appear so likely, since, although such rearrangements have been postu-

lated[14,15] and found[15] to occur in photochemically excited species, they are virtually absent in ground-state solution chemistry.[16-18] Such a radical process is, however, not excluded by the experimental evidence.

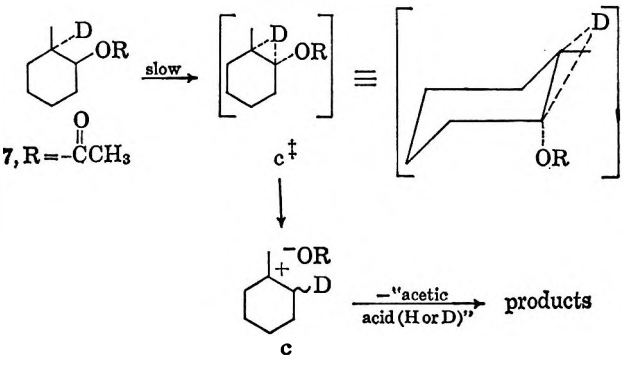
Also pertinent to any discussion of liquid phase *vs.* surface-catalyzed pyrolysis reactions is the observed close similarity of percentage of the two olefins (Table I) in the pyrolysate from *trans* xanthate **2** irrespective of the pyrolysis conditions (seasoned or unseasoned stainless steel or Pyrex tube at 250° or in the liquid phase at 200°). The *cis* xanthate (**1**), by contrast, is more sensitive (Table I) to the nature of the pyrolysis conditions, particularly the surface employed (Pyrex or stainless steel), and to the presence of acidic carbonaceous residues[19] which accumulate after extensive seasoning of the reactor. These latter deposits are presumably responsible[19] for the large proportion of net *trans* elimination both in xanthate **1** and *cis* acetate **3**, possibly through the increased intervention of heterogeneous ionic reaction paths.

The pyrolyses of *cis*-[19,20] (**3**) and *trans*-2-methylcyclohexyl acetate[20] (**4**) have been examined previously and the results in Table I are in close agreement with the values obtained by these earlier workers. Again as for *trans* xanthate **2**, the olefinic ratio from *trans* acetate **4** is nearly independent of the pyrolysis conditions, whereas that from *cis* acetate **3** exhibits greater dependence. The presence of carbonaceous deposits has a profound effect[19] (Table I) on the ratio of olefinic products produced in the pyrolysis of *cis* acetate **3**, resulting in an up to sixfold increase in the amount of 1-methyl-1-cyclohexene, the product from net *trans* elimination, under our experimental conditions.

In a manner analogous to that employed[13] in the xanthate series, values of k_D/k_H for the elimination reaction of the acetates **3** and **4** may be determined from the pyrolytic data (Table I) for the d_0 and 2-d_1 compounds. The values found for this process are 0.67 and 0.53–0.56, respectively, in fairly good agreement with those (0.50–0.59) previously reported in the literature.[4,13] Particularly interesting is the relative constancy of the value of k_D/k_H for *cis* acetate **3** (Table I) even in the presence of carbonaceous impurities.

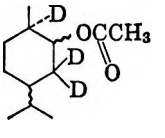
The close similarity of these pyrolytic k_D/k_H values for acetates **3** and **4** as opposed to the striking differences exhibited by xanthates **1** (1.0) and **2** (0.59–0.72) might at first suggest that in the acetates the concerted *cis*-cyclic mode of elimination is operative. However, examination of the isotopic content of the resulting olefinic products (Table I) from the deuterated compounds **7** and **8** does not support this view. While the data for the *trans* acetate (**8**) are consistent with expectations for a homogeneous *cis*-cyclic elimination process, the results for the *cis* acetate (**7**) are again anomalous. In this latter compound, 78% of the 1-methyl-1-cyclohexene produced (6% of the total olefinic product) still retains the deuterium label. One possible mechanism which might be expected to yield such isotope effect and label retention data may be visualized as **7** → c‡ → c → products. An analogous 1,2 participation of an axial hydrogen has been postulated to account for the 77-fold rate increase in the ethanolysis of 2-methylcyclohexyl tosylate on passing from the *trans* to the *cis* series.[21] (See Scheme III.)

SCHEME III



The failure of *cis* xanthate **5** to exhibit an isotope effect, interpreted as indicating spontaneous heterolysis of the C–O bond in the activated complex without requiring neighboring deuterium assistance (as was invoked in c‡ in *cis* acetate **7**), may well be a reflection of the greater acid strength[4] (and stability of the anionic species) predicted for the unknown xanthic acid compared with that of normal carboxylic acids.

Again, as for xanthates **1** and **5**, it cannot be stated with absolute certainty that these are completely homogeneous pyrolytic reactions in acetates **3** and **7**; however, in this case, the relative insensitivity of the product ratios (Table I) to tube wall construction (Pyrex or coated stainless steel) would suggest that this might be so. Particularly reassuring is the observation without comment of the analogous rearrangement process[22] in the pyrolysis of an isomer mixture of 1,3,3-d_3-carvomenthyl acetate (**21**) over glass helices at 400°.



21

Thus it appears that, under the pyrolysis conditions employed in this study, the olefinic products from effective *trans* elimination in the 2-methylcyclohexyl-S-methyl xanthates and acetates may be adequately accounted for by postulating, as the major process, spontaneous (xanthates) or neighboring hydrogen

(14) (a) G. W. Griffin, J. Covell, R. C. Petterson, R. M. Dodson, and G. Close, *J. Amer. Chem. Soc.*, **87**, 1410 (1965); (b) H. Kristinsson and G. W. Griffin, *ibid.*, **88**, 378 (1966); (c) G. W. Griffin, A. F. Marcantonio, H. Kristinsson, R. C. Petterson, and C. S. Irving, *Tetrahedron Lett.*, 2951 (1965).

(15) D. I. Schuster and I. S. Krull, *J. Am. Chem. Soc.*, **88**, 3456 (1966).

(16) C. Walling in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 416 ff.

(17) L. H. Slaugh, *J. Amer. Chem. Soc.*, **81**, 2262 (1959).

(18) D. Y. Curtin and J. C. Kauer, *J. Org. Chem.*, **25**, 880 (1960).

(19) Similar effects of acidic carbonaceous residues have been reported by W. J. Bailey and L. Nicholas [*J. Org. Chem.*, **21**, 854 (1956)] in their pyrolysis studies on *cis*-2-methylcyclohexyl acetate.

(20) R. T. Arnold, G. G. Smith and R. M. Dodson, *ibid.*, **15**, 1256 (1950).

(21) (a) W. Hückel and H. D. Sauerland, *Ann.*, **592**, 190 (1955); (b) A. Streitwieser, Jr., "Solvolytie Displacement Reactions," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 143.

(22) A. G. Thomas and B. Willhalm, *J. Chem. Soc., Sect. B*, 219 (1966).

assisted (acetates) heterolysis of the C–O bond yielding ion pairs, followed by direct proton loss or 1,2-hydride shift and subsequent proton loss from the cationic species.

Experimental Section[23]

Preparation of d_0- and 2-d_1-Labeled Xanthates and Acetates (1–8) and 2,6,6-d_3-2-Methylcyclohexyl-S-methyl Xanthate (20).—These materials were prepared and characterized as described earlier.[3]

Pyrolysis of *trans*-2-Methylcyclohexyl-S-methyl Xanthate (2) and 2,6,6-d_3-2-Methylcyclohexyl-S-methyl Xanthate (20) in the Liquid Phase.—The crude xanthate (containing a fair amount of dimethyl trithiocarbonate as an impurity) was pyrolyzed over powdered soft glass in a flask equipped with a nitrogen inlet tube and a Vigreux column by heating in a Wood's metal bath at 200–210°.[24] The pyrolysate was collected in a Dry Ice–isopropyl alcohol cooled trap. In each case, the pyrolysate was analyzed by vpc on a 15% Apiezon L column (10 × 0.25 in.) at 100°.

The pyrolysate from xanthate **20** was separated by preparative vpc employing the above conditions and the material corresponding in retention time to 3-methyl-1-cyclohexene (or methylenecyclohexane) was examined by nmr spectroscopy. The spectrum of this compound exhibited as its main features a signal centered at δ 5.55 ppm (1 H, HC=C) and a closely spaced doublet (J = 1 cps) centered at δ 0.95 ppm (3 H, $-CH_3$). No signals were apparent for either terminal methylene (δ 4.6) or cyclopropane hydrogens (δ <1.0) in this material, nor was evidence found for the presence of cyclopropane hydrogens[3] in the nmr spectrum of the 1-methyl-1-cyclohexene fraction from this pyrolysis.

Conditions for All Other Pyrolysis Studies on 2-Methylcyclohexyl Acetates and S-Methyl Xanthates.—All pyrolyses were carried out in a Varian Aerograph Model 202A gas chromatograph fitted with either a 2 ft × 0.25 in. Greenville Tube, Inc., Type 304, W & D stainless steel tube equipped with a small plug of Pyrex glass wool at the entrance (and previously seasoned by *ca.* 30 pyrolyses of 10-μl samples of xanthates and acetates under the conditions listed below) or a 2 ft × 6 mm length of no. 7740 Pyrex tube with a small plug of Pyrex glass wool at the entrance. In both cases injector liners of 2-mm Pyrex tube were employed. The temperature conditions were as follows: xanthates, injector block 175°, column 250°, detector block 150°, helium flow *ca.* 20–60 ml/min over 5 min, estimated contact time with hot zone 0.5–1 min, sample size 2–10 μl; acetates, injector block 175°, column 400°, detector block 150°, helium flow conditions *ca.* 15–25 ml/min over 5 min, estimated contact time with hot zone 0.5–1 min, sample size 2–10 μl.

General Procedure.—The sample was injected at the requisite temperature and minimum flow rate. After 2 min, the flow rate was raised uniformly to the maximum value over the ensuing 3 min. The pyrolysate was collected in a 4-mm glass U-tube with liquid nitrogen cooling. When visible evidence of continued pyrolysate flow had ceased, the tube was removed, 20 μl of anhydrous ether added, and the sample examined by analytical gas chromatography on 20% Apiezon L column (10 ft × 0.25 in.) at 100°. Preparative gas chromatography employing the same conditions yielded the pure isomeric olefins whose isotopic contents were determined from the molecular ion regions of the 70-eV mass spectra. Olefinic compositions were determined by the cut and weigh method on the analytical vpc traces.

Registry No.—**1**, 15288-12-7; **2**, 15288-13-8; **3**, 15288-14-9; **4**, 15288-15-0; **5**, 15288-22-9; **6**, 15288-17-2; **7**, 15285-97-9; **8**, 15285-91-3; **20**, 15296-85-2.

Acknowledgment.—We should like to thank Professor J. I. Brauman for helpful and stimulating discussions during the preparation of this manuscript.

(23) All compounds were purified by vapor phase chromatography (vpc) and characterized by infrared spectroscopy and mass spectrometry as described in ref 3. Olefinic products were analyzed and purified by vpc on a Varian Aerograph Model 202B chromatograph employing the columns listed. Mass spectra of olefinic products were recorded by Dr. A. M. Duffield on an Atlas CH-4 mass spectrometer equipped with a Model TO-4 ion source and heated gas cartridge inlet system maintained at 200°. Ionizing conditions are as follows: ion source temperature, 200°; ionizing voltage, 70 eV; and ionizing current, 10 μA. Nmr spectra were run by Dr. Y. Kanazawa and Mr. R. C. Ronald on a Varian Associates Model A-60 spectrometer in deuteriochloroform solution and using tetramethylsilane (δ 0.00) as an internal standard.

(24) Pyrolysis of xanthate **20** containing dimethyl trithiocarbonate under these conditions and that of a purified sample in the absence of powdered soft glass and with the bath temperature maintained at 250° yielded identical results.

Ozonolysis. X. The Molozonide as an Intermediate in the Ozonolysis of *cis* and *trans* Alkenes[1a]

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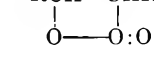
Low temperature (−130°) nmr spectral studies of the ozonation mixtures which were prepared from dichlorodifluoromethane solutions of the stereoisomers of 2-butene, 2-pentene, and 3-hexene gave evidence for the existence of molozonides. The *cis* molozonides could be observed to decompose at −130° to the usual ozonolysis products, whereas the *trans* molozonides required warming to −100° before they were converted into the usual ozonolysis products.

It was Staudinger[2] who first made the suggestion that the observed alkene–ozone reaction products were actually secondary reaction products which arose from a primary addition product. By analogy to the moloxide which at that time was postulated as the primary autoxidation product of alkenes and which was formulated as a 1,2-dioxetane, he called the primary alkene–ozone reaction product a molozonide and formulated it as



It was not until 1960 that firm, indirect experimental evidence for the existence of the molozonide appeared when Criegee and Schröder,[3] reported that treatment of the ozonation mixture from *trans*-di-*t*-butylethylene with isopropyl Grignard reagent gave rise to *dl*-2,2,5,5,-tetramethylhexane-3,4-diol. Subsequently, it

(1) (a) A preliminary report on part of this work has been published: L. J. Durham and F. L. Greenwood, *Chem. Commun.*, 843 (1967). (b) F. G. is indebted to the Chemistry Department, Stanford University, and particularly to Dr. H. S. Mosher, for their hospitality and to the Petroleum Research Fund of the American Chemical Society for partial financial support during sabbatical leave from Tufts University.

(2) H. Staudinger, *Ber.*, **58**, 1088 (1925).

(3) R. Criegee and G. Schröder, *Chem. Ber.*, **93**, 689 (1960).

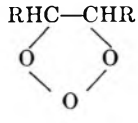
TABLE I

NMR SPECTRAL DATA FOR *trans* ALKENE OZONATION MIXTURES[a]

Alkene	Aldehyde CHO, δ[b]	Ozonide CH, δ	Molozonide CH, δ	Propanal CH_2, δ	Ethanal CH_3, δ	Methylene, δ	Methyl, δ
			−130° Spectra				
trans-2-Butene	9.52 (d)	5.00 (q), 4.90 (q)[c]	4.12 (q)		1.98 (d)		1.15 (d)
trans-2-Pentene	9.62 (s)	4.95 (u)	4.08 (m)	2.38 (u)	2.05 (d)	1.52 (m)	1.27 (d), 0.85 (t)
trans-3-Hexene			4.07 (t)			1.60 (m)	0.90 (t)
			−70° Spectra				
trans-2-Butene	9.55 (d)	5.07 (q), 4.98 (q)[d]			1.97 (d)		1.13 (d)
trans-2-Pentene	9.57 (s)	4.98 (m)[d]		2.27 (q)	1.95 (d)	1.47 (u)	1.22 (d), 0.82 (t)
trans-3-Hexene	9.60 (s)	4.93 (t), 4.87 (t)[d]		2.27 (q)		1.48 (m)	0.80 (t)

[a] Authentic ozonides of 2-butene and 3-hexene, authentic 3-hexene ozonation oligomer, and aldehydes were used for peak assignments. [b] All δ values related to internal Me_4Si = 0.00. $CHCl_2F$ was used as an internal standard. Abbreviations used were (d) doublet, (m) multiplet, (q) quartet, (s) singlet, (t) triplet, (u) unresolved. [c] Oligomer evidenced by weak absorption on low field side of peak. [d] Marked absorption, which disappeared on recooling the mixture to −130°, on low field side of peak indicated considerable oligomer.

was reported[4] that α-diols could be isolated from a variety of other alkenes by ozonation of the alkene in ether solution at −115° and treatment of this reaction mixture with the isopropyl Grignard reagent. By this reaction sequence with the geometric isomers of the lower alkenes, the α-diols which would result from the stereospecific *cis* addition of ozone to the *trans* alkenes were isolated in good yield, but no α-diol could be obtained from the *cis* alkenes. These data supported the molozonide as a stable species under the proper conditions in the case of *trans* and a few other alkenes. The structure of the *trans* molozonide as a 1,2,3-trioxolane



appears rather well established by the obtention of α-diols of the proper configuration[3,4] and by the more recent nmr spectral study of Bailey, *et al.*[5] Some crude evidence has appeared[4b] that the *cis* molozonide may be formed by the reaction of a *cis* alkene and ozone, and that the *cis* molozonide was less stable than the corresponding *trans* isomer. Other than this crude evidence, however, experimental data supporting the existence of the *cis* molozonide has not been published.

The data that have appeared on the molozonide indicate that it can be an observable alkene–ozone reaction product, but the data do not necessarily prove that the molozonide is an intermediate in the ozonolysis of alkenes. This paper reports the results of low temperature nmr spectral studies which support the formation of the molozonide as an intermediate in the ozonolysis of both *cis* and *trans* alkenes.

In these studies the crucial region for observation was the methine proton region. The −130° nmr spectrum (*cf.* Table I) of the ozonation mixture which was prepared from *trans*-3-hexene had one methine triplet at δ 4.07 which can be assigned to the *trans* molozonide methine protons. After 7 hr at −130° the spectrum of such a solution was identical with the spectrum initially recorded. The −130° spectrum from *trans*-2-pentene had a very weak methine absorption at δ 4.95 which may be assigned to ozonide methine

TABLE II

NMR SPECTRA OF REFERENCE COMPOUNDS[a]

Compd	Aldehyde CHO, δ[b]	Methine, δ	Methylene, δ	Methyl, δ
cis-3-Hexene		5.30 (t)	2.05 (m)	0.98 (t)
Ethanal	9.42 (q)			1.83 (d)
Propanal	9.50 (t)		2.20 (q)	0.85 (t)
2-Butene-ozonide[c]		5.23 (q), 5.17 (q)		1.27 (d)
3-Hexene ozonide[c]		5.03 (t), 4.98 (t)	1.67 (m)	0.95 (t)
3-Hexene ozonation oligomer[c]		5.73–4.83 (u)	1.72 (m)	0.97 (t)

[a] Spectra of 8% solutions in dichlorodifluoromethane recorded at −50°. [b] *Cf.* footnote *b*, Table I. [c] For preparation, *cf.* ref 6.

by comparison with the methine absorption of authentic ozonides (*cf.* Table II); the principal methine absorption was at δ 4.08 (molozonide), and weak absorptions indicative of ethanal and propanal were also present. With *trans*-2-butene the areas of the ozonide and molozonide methine peaks indicated that these two components were present in the ratio 1.0:3.1, ethanal was clearly present, and weak absorption on the low-field side of the ozonide methine peak indicated a small amount of oligomer. The methine absorption of the alkene ozonation oligomer was broad and overlapped the ozonide methine absorption, but the former extended further downfield than did the latter (*cf.* Table II). The spectra from *trans*-2-pentene and *trans*-2-butene did not change as long as the ozonation mixtures were kept at −130°. These data indicated that these *trans* molozonides were stable at −130°. They also suggest that with a certain portion of the smaller alkene molecules the energy liberated during the formation of the molozonides could not be dissipated sufficiently rapidly in the small molecule and into its environment with the result that these species continued to react to give ozonolysis products. One might expect to observe this phenomenon with higher alkenes if the alkene and ozone concentrations used for the ozonation were sufficiently high. The single molozonide methine quartet that was observed with *trans*-2-butene and the single molozonide methine triplet that was observed with *trans*-3-hexene provide additional support for the 1,2,3-trioxolane structure of the molozonide.

The decomposition of the molozonide was observed by projecting the molozonide methine peak and the

(4) (a) F. L. Greenwood, *J. Org. Chem.*, **29**, 1321 (1964); (b) F. L. Greenwood, *ibid.*, **30**, 3108 (1965).

(5) P. S. Bailey, J. A. Thompson, and B. A. Shoulders, *J. Amer. Chem. Soc.*, **88**, 4098 (1966).

TABLE III

NMR SPECTRAL DATA FOR *cis* ALKENE OZONATION MIXTURES[a]

Alkene	Aldehyde CHO, δ[b]	Ozonide CH, δ	Molozonide CH, δ	Ethanal CH_3, δ	Methylene, δ	Methyl, δ
			−130° Spectra			
cis-2-Butene	9.50 (u)	5.05 (q), 4.97 (q)[c]	4.52 (u)[e]	1.80 (d)		1.17 (d), 1.08 (d)
cis-2-Pentene	9.65–9.56 (m)	4.93 (m)[c]	4.35 (m)		Overlapping multiplets	2.02–0.42
cis-3-Hexene		4.95 (t), 4.87 (t)[c]	4.53 (u)[e]		1.48 (u)	0.80 (u)
			−50° Spectra			
cis-2-Butene		5.17 (q), 5.10 (q)[d]		1.93 (d)		1.23 (d)
cis-2-Pentene		5.70–4.80 (m)[d]			2.27–1.30 (m)	1.27 (d), 0.87 (t)
cis-3-Hexene		5.05 (t), 5.00 (t)[d]			1.58 (m)	0.88 (t)

[a–d] *Cf.* footnotes, Table I. [e] Gianni, *et al.*,[7a] have observed multiplicity of *cis* vicinal methine absorption in other cyclic systems.

ozonide methine region on an oscilloscope. With all three *trans* alkenes the molozonide peak did not begin to disappear until the mixture was warmed. As the temperature of each ozonation solution reached −100° the ozonide methine peak began to appear downfield from the molozonide peak. The former could be observed to increase as the latter diminished, and when a temperature of −90° was reached the molozonide peak had disappeared completely. The solutions were warmed to −70°, and their nmr spectra verified the usual[6] ozonolysis products of ozonide, aldehyde, and oligomer (*cf.* Table I). The presence of considerable oligomer in the ozonation mixtures was indicated by marked absorption on the low field side of the ozonide methine peak in the −70° spectra and the virtual disappearance of this absorption when the mixtures were recooled to −130°. This behavior may be explained by oligomer coming into and going out of solution.

The first spectra at −130° were taken about 30 min after the start of the ozonation. With all of the *cis* alkenes the two methine absorptions (*cf.* Table III) in the first spectra indicated the presence of both ozonide and molozonide; now, however, the molozonide methine absorption was at a lower field than in the case of the *trans* molozonides. These ozonation mixtures were kept at −130°, and the spectra were recorded at various times. The molozonide methine absorption diminished as the ozonide methine absorption increased, and the areas of these peaks were used to obtain an approximation of the relative amounts of ozonide and molozonide in the mixtures. Illustrative data are recorded in Table IV. After the disappearance of the molozonide methine absorption, the ozonation mixtures were warmed to −50° and the spectra indicated the presence of ozonide and oligomer. Again, the oligomer in each case was indicated by weak absorption on the low field side of the ozonide methine peak of the −130° spectra, a marked increase in intensity of this low field absorption in the −50° spectra, and the near loss of this absorption when the ozonation mixtures were recooled to −130°. Under the usual ozonation conditions, *cis* alkenes gave little aldehyde;[6] in these ozonations the only clear evidences of aldehyde were those shown in Table III. The larger amount of oligomer in these ozonations is interesting in light of the fact that *cis* alkenes on ozonation under usual conditions gave rise to little oligomer, whereas with *trans* alkenes oligomer was the principal product.[6] It has been suggested[6] that the

(6) F. L. Greenwood and H. Rubinstein, *J. Org. Chem.*, **32**, 3369 (1967).

TABLE IV

OZONIDE/MOLOZONIDE RATIOS IN *cis* ALKENE OZONATION MIXTURES

Alkene	Minutes after start of ozonation	Ozonide/molozonide
cis-2-Butene	31	1.00:0.67
	68	1.00:0.11
cis-2-Pentene	39	1.00:1.32
	60	1.00:0.75
	121	1.00:0.20
cis-3-Hexene	25	1.00:0.57
	49	1.00:0.09

molozonide is the principal source of the ozonation oligomer, and that the different behaviors of *cis* and *trans* alkenes may be explained by the relative stability of *cis* and *trans* molozonides. If the experimental conditions were such that the *cis* molozonide were stable for some time, then one might expect reasonable amounts of oligomer from the ozonation of *cis* alkenes. The presently reported data support this thesis.

The 1,2,3-trioxolane structure for the *trans* molozonide would appear to be rather firmly established. There are a number of instances[7] where, with cyclic compounds having vicinal methine protons, the *cis* isomer absorbs at a lower field than does the *trans* isomer. This pattern is followed uniformly by the *cis* and *trans* molozonides (*cf.* Tables I and III). The chemical shift of the methine proton of the *cis* molozonide differs from that of the *trans* isomer by approximately the same amount that has been observed in other ring systems.[7] This suggests that the *cis* molozonide has the same ring system as the *trans* isomer rather than a ring system of a different size. It is not really known, but the σ structure might not be expected for the *cis* molozonide which had been suggested by Murray, *et al.*,[8] to exhibit the varied stabilities which were observed with the *cis* molozonides (*cf.* Table IV). Simply by analogy with the *trans* molozonide we favor the 1,2,3-trioxolane structure for the *cis* molozonide.

The data of Table IV indicate some differences in stability of the various *cis* molozonides. The high initial ozonide/molozonide ratio which was observed with *cis*-2-butene may be explained by considerable formation of ozonide during the alkene–

(7) (a) M. H. Gianni, E. L. Stogryn, and C. M. Orlando, Jr., *J. Phys. Chem.*, **67**, 1385 (1963); (b) D. Y. Curtin, H. Gruen, Y. G. Hendrickson, and H. E. Knipmeyer, *J. Amer. Chem. Soc.*, **83**, 4838 (1961); (c) F. A. L. Anet, *ibid.*, **84**, 747 (1962).

(8) R. W. Murray, R. D. Youssefyeh, and P. R. Story, *ibid.*, **89**, 2429 (1967).

ozone reaction (*cf.* comments on *trans*-2-butene–ozone reaction). Once the decomposition of this molozonide began to be observed, however, it did so at roughly the same rate as the *cis* molozonide of 2-pentene, the most stable of the *cis* molozonides that were studied. In considering the stability of the 1,2,3-trioxolane system, two factors may be involved. First, one has a system that is inherently unstable. Examination of Briegleb models indicates that a steric factor must also be considered. The experimental facts[4b,5] would indicate that alkyl groups in a *trans* configuration in a 1,2,3-trioxolane effect no instability in the molecule, and models support the absence of interaction between the alkyl groups of such a configuration. With the alkyl groups in a *cis* configuration in such a system, however, models suggest interaction of the alkyl groups. This interaction becomes of some consequence with two ethyl groups, and one might predict that, with *cis* alkenes having groups larger than ethyl, the stability of the *cis* molozonide will be markedly less than that observed for the *cis* molozonide of 3-hexene.

In the studies[4] with the *trans* isomers of 2-butene, 2-pentene, and 3-hexene the α-diols that were obtained were entirely of the configuration that one would expect from the stereospecific *cis* addition of ozone to the carbon–carbon double bond. The current studies supported the stereospecific *cis* addition of ozone to both *cis* and *trans* alkenes. The methine absorptions of the two molozonide stereoisomers were quite different (*cf.* Tables I and III). In the $-130°$ spectra that were obtained from the *trans* alkene ozonation mixtures there was no indication of *cis* molozonide methine absorption, and, likewise, in the $-130°$ spectra which were obtained from the *cis* alkene ozonation mixtures there was no indication of *trans* molozonide methine absorption.

It has been mentioned previously[7] that *cis* vicinal methine protons in cyclic systems absorb at a lower field than do *trans* ones, and the molozonides examined in this work follow this pattern. If one assumes that the same phenomenon will be exhibited by 1,3-methine protons in cyclic systems, then one has an indirect method of assigning stereochemical configurations to ozonides. In the nmr spectrum of authentic 2-butene ozonide[6] the peak height of the lower field methine quadruplet is about half that of the higher field methine quadruplet. In vapor phase chromatography of this same ozonide[9] the peak area of the steroisomer of longer retention time is about half that of the stereoisomer of shorter retention time. Thus, one may make the assignment that the *cis* ozonide is the one of longer retention time in gas chromatography and the one of lower field methine absorption in the nmr spectrum. This assignment is in agreement with that already made by Murray, *et al.*[10] A number of other instances where the methine absorption of a *cis* ozonide is at lower field than that of the corresponding *trans* isomer have been published.[8]

If one assumes that peak height and peak area in an nmr spectrum are directly proportional, then one can obtain an approximation of the *cis*/*trans* ratio of the ozonides produced in the presently reported ozonolyses. In the $-70°$ spectrum of the *trans*-3-hexene ozonation mixture and the $-50°$ spectrum of the *cis*-3-hexene ozonation mixture the methine triplets of the stereoisomeric ozonides were well resolved and of equal heights. Thus, where the molozonide is clearly rearranging to ozonide in dichlorodifluoromethane solvent each alkene stereoisomer gave the stereoisomeric ozonides in about a 50:50 ratio. In the spectra obtained from the 2-butene ozonation mixtures the methine quadruplets were not completely resolved, but were resolved sufficiently well that one could calculate an approximate *cis*/*trans* ozonide ratio. From the $-70°$ spectrum of the *trans*-2-butene the *cis*/*trans* ozonide ratio was 31:69. From the first $-130°$ spectrum from *cis*-2-butene the *cis*/*trans* ozonide ratio was 31:69, and, from the last $-130°$ spectrum, when nearly all of the molozonide had disappeared, the *cis*/*trans* ozonide ratio was 33:67. These data may be added to those already published[9,11] which show that experimental conditions, particularly solvent, have a marked effect on the *cis*/*trans* ozonide ratio formed in alkene ozonolyses. It is impossible to draw any conclusions about the ozonide which was formed in the 2-pentene ozonations. If this alkene behaved here as under other ozonation conditions,[9,12] it gave rise to stereoisomeric pairs of three different ozonides. The methine protons of all of these absorb in the same region, and it was impossible to draw any conclusions from the complex pattern of the methine region of the 2-pentene ozonation spectra.

Experimental Section

The 2-pentenes and 3-hexenes were API standard samples. The 2-butenes (CP grade) and the fluorocarbons were purchased from Matheson Scientific Co.

An ozonizer of the type described by Bonner[13] at an oxygen flow rate of 1.35 l./hr produced 2–3 vol % ozone. Spectra were recorded with a Varian HR-60, Model 4300-B, using a V-4331 nmr probe which was equipped with a V-4340 variable-temperature modification. The theoretical amount of ozone was introduced into an nmr tube, which was immersed in a $-130°$ bath, containing 0.30 ml of liquid dichlorodifluoromethane, 0.24 mmol of alkene, and a small amount of dichlorofluoromethane as an internal standard. After the ozonation, helium was bubbled through the reaction mixture for 10 min to remove dissolved oxygen, and the nmr tube was then transferred to the probe which was precooled to $-130°$. With the *cis* alkenes, spectra were recorded at $-130°$ at intervals until the molozonide methine absorption disappeared. The ozonation mixtures were then warmed to $-50°$, and the spectra were recorded at this temperature. With the *trans* alkenes the spectra were recorded at $-130°$. The molozonide methine peak and the ozonide methine region were projected onto an oscilloscope, and the ozonation mixtures were warmed slowly to observe the molozonide–ozonide rearrangement. The mixtures were then warmed to $-70°$ and the spectra were recorded.

Registry No.—*trans*-2-Butene molozonide, 15981-77-8; *trans*-2-pentene molozonide, 15981-76-7; *trans*-3-hexene molozonide, 2028-40-2; *cis*-2-butene molozonide, 15981-73-4; *cis*-2-pentene molozonide, 15981-74-5; *cis*-3-hexene molozonide, 2946-58-9.

(9) F. L. Greenwood, *J. Amer. Chem. Soc.*, **88**, 3146 (1966).
(10) R. W. Murray, R. D. Youssefyeh, and P. R. Story, *ibid.*, **88**, 3655 (1966).
(11) *Cf.* references cited in ref 8.
(12) L. D. Loan, R. W. Murray, and P. R. Story, *J. Amer. Chem. Soc.*, **87**, 737 (1965).
(13) W. A. Bonner, *J. Chem. Educ.*, **30**, 452 (1953).

Aprotic Diazotization[1] of Arylamines in Aromatic Solvents. The Effect of Addition of Strong Acid[2]

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The reaction of arylamines with amyl nitrite in aromatic solvents gives moderate yields of biaryl products. Substrate and positional selectivity, as well as the iodine-abstracting ability of the intermediate generated, indicate that a phenyl radical is the attacking species. The addition of strong acid to the system results in a change in the reaction scheme wherein partial participation of a phenyl cation or diazonium ion is involved. The reaction has been adapted for synthetic use to give biaryl products, supplementing the work of previous investigators.

The reaction of aromatic amines with amyl nitrite in aromatic solvents gives moderate yields of biaryl products.[4] While the present investigation, initiated to determine the mechanism(s) involved and the synthetic scope of the reaction, was in progress, it was reported[5] that phenyl radicals are involved in this reaction. The nature of the results reported herein further supports the intermediacy of radicals and complements the proposed mechanistic scheme for the course of biaryl formation by diazotization coupling[6] reactions.

To determine optimum reaction conditions, *o*-chloroaniline was diazotized with a slight excess of amyl nitrite in a 30-fold molar excess of benzene. Order and method of addition of reagents, temperature, and nitrite concentration were varied without affecting the biaryl yield (Table I). The choice of conditions was then based on convenience; the reagents were added to excess solvent at room temperature and reaction was effected at reflux or 120°, whichever temperature was lower. Nitrogen evolution, a means of observing the decomposition process, ceased within 2 hr.

TABLE I

DIAZOTIZATION OF *o*-CHLOROANILINE IN BENZENE

Technique[a]	Temperature, °C	Time, hr	% yield
Nitrite added to amine–benzene	80[b]	4	38
Amine added to nitrite–benzene	80	4	40
Nitrite, amine, benzene mixed directly	~27	4	39
Nitrite, amine, benzene mixed directly	80	3	40
Nitrite,[c] amine, benzene mixed directly	80	3	40

[a] 1.2 molar equiv of nitrite present. [b] Solution reflux temperature. [c] 2.0 molar equiv of nitrite present.

The extent of nitrogen evolution was measured in two reactions to determine whether the limited formation of biaryl product was due to incomplete diazotization and/or subsequent decomposition of the intermediate. In both cases, more than 90% of the theoretical gas yield was observed, indicating that the low biaryl yield is a result of competition from side reactions.

Utilization of this method for preparative purposes (~1 *M*) was successful. For example, *m*- and *p*-methylbiphenyl were obtained in 30 and 40% yield, respectively, from reaction of the appropriate toluidines in benzene. The isomeric chlorobiphenyls were prepared in 30% yield from the chloroanilines and a 12% yield of 2,5-dimethylbiphenyl was isolated on diazotization of aniline in *p*-xylene.

The reaction was conducted in a variety of aromatic solvents under the conditions described above. The isomer distributions, high *ortho* and *para* and low *meta* substitution, are characteristic of radical attack[7] (Table II).

TABLE II

COMPOSITION OF BIARYL PRODUCTS FROM APROTIC DIAZOTIZATION OF ANILINE IN SUBSTITUTED BENZENE

Substrate	% yield	Substituted biphenyl— *o*	*m*	*p*
Toluene[a]	28.8	57.1	28.0	14.0
Nitrobenzene[b]	36.0	44.9	15.4	39.8
Chlorobenzene[b]	40.7	55.0	27.5	17.5
Bromobenzene[b]	47.8	48.1	33.9	17.9
Methyl benzoate[b]		51.4	18.6	29.7

[a] At reflux. [b] At 120°.

Recently, the ability of aryl radicals, generated from benzoyl peroxide, to abstract iodine from aryl iodides was demonstrated.[8] Thus, this is an additional device to determine the amount of radical intermediates generated from the aprotic diazotization of an arylamine. The excellent correlation of yield of aryl iodide from both aprotic diazotization and aroyl peroxide decomposition not only supports the presence of phenyl radicals in the amine–amyl nitrite system but confirms that these are the major arylating agents (Table III). Aryl cations do not display this abstracting ability; *e.g.*, decomposition of benzenediazonium tetrafluoroborate under these conditions does not give any iodine abstraction product.[9]

To determine the nature of the arylating agent generated from the diazotization of aniline in the presence of an equivalent of strong acid, the isomer

(1) Aprotic refers to solvents that are not proton donors. Other examples of such diazotization are summarized by D. Y. Curtin, J. A. Kampmeier, and B. R. O'Connor, *J. Amer. Chem. Soc.*, **87**, 863 (1965).

(2) Financial support (Grant No. GP-3976) from the National Science Foundation is gratefully acknowledged.

(3) National Science Foundation Graduate Trainee.

(4) (a) J. I. G. Cadogan, *J. Chem. Soc.*, 4257 (1962). (b) Previous reports on the use of the method in preparative applications (*cf.* ref 4a) is limited to reactions at <0.1 mol scale. This investigation extends the scale to 1 mol with appropriate modifications of conditions and isolation techniques.

(5) J. I. G. Cadogan, D. A. Roy, and D. M. Smith, *J. Chem. Soc., Sect. C*, 1249 (1966).

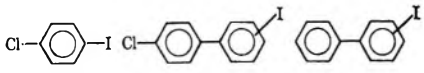
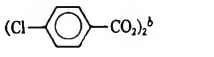
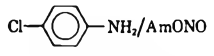
(6) C. Rüchardt and E. Merz, *Tetrahedron Lett.*, **36**, 2431 (1964).

(7) H. Zollinger, "Azo and Diazo Chemistry," Interscience Publishers, Inc., New York, N. Y., 1961, p 157.

(8) (a) D. L. Brydon and J. I. G. Cadogan, *Chem. Comm.*, 744 (1966); (b) J. F. Bunnett and C. C. Wamser, *J. Amer. Chem. Soc.*, **88**, 5534 (1966).

(9) (a) Decomposition of benzenediazonium tetrafluoroborate was also carried out in ethylene chloride and glyme with either iodine or *m*-chloroiodobenzene present. In no case was iodobenzene observed. However, from the reaction in glyme significant amounts of the ether cleavage products, anisole and β-methoxyethyl phenyl ether, were obtained, indicating that the cation becomes free of the gegenion: P. Caruso and L. Friedman, unpublished data. (b) For examples of alkyl diazonium ions, see A. T. Jurewicz, J. H. Bayless, and L. Friedman, *ibid.*, **87**, 5788 (1965).

TABLE III
EXTENT OF IODINE ABSTRACTION BY REACTION INTERMEDIATES[a]

Precursor	% yield		
			
 [b]	76	8	39
	75		21

[a] The ratio of the precursor to iodobenzene was 1.0:22.4. [b] Data from ref 8b.

distributions of biaryl products formed on reaction of a variety of precursors in nitrobenzene and bromobenzene were obtained. The reactions studied ranged from the decomposition of benzoyl peroxide (radical intermediate) to the decomposition of benzenediazonium tetrafluoroborate (cationic arylating species).[10] In addition, the relative reactivity of several of these intermediates in benzene–nitrobenzene mixtures was determined (Table IV).

TABLE IV
RELATIVE REACTIVITY AND ISOMER DISTRIBUTIONS FROM REACTIONS IN NITRO- AND BROMOBENZENE AT 78°

Precursor	K_{NO_2}/K_H	Nitrobiphenyls o	m	p	Bromobiphenyls o	m	p
$C_6H_5NH_2$/AmONO	3.04	51	13	36	53	28	19
$C_6H_5N(NO)COCH_3$		50	13	37	58	25	18
$C_6H_5N_2^+BF_4^-/C_6H_5N$[a]	2.72	53	14	33	55	26	19
$(C_6H_5CO_2)_2$	2.90[a]	60	10	30	54	28	18
$C_6H_5N_2^+Cl^- \cdot H_2O$		27	58	15	47	18	35
$C_6H_5NH_3^+Cl^-$/AmONO	0.58	25	58	17			
$C_6H_5N_2^+Cl^-$		26	55	19			
$C_6H_5N_2^+BF_4^-$[a]	0.35	20	80	0	56	20	24

[a] Data from ref 10.

Both the relative reactivity and positional selectivity of the intermediate generated in the aniline–amyl nitrite system compare favorably with the values obtained from acknowledged radical sources.[11] However, the results obtained from the reaction of aniline hydrochloride cannot be easily interpreted. Although the relative reactivity (less than unity) and the isomer distribution (high *meta* product) indicate participation by a cationic arylating agent, there is only partial correspondence with results obtained from the benzenediazonium tetrafluoroborate decomposition. Involvement of phenyl radical can partially account for this discrepancy. However, it is not possible to compute the observed isomer distribution exactly by attributing fractions of the phenylation to radical and cationic intermediates.[12]

(10) (a) R. A. Abramovitch and J. G. Saha, *Tetrahedron*, **21**, 3297 (1965). (b) The comparison of data from the literature (*cf.* ref 10a) was made only where all reaction conditions were similar. In addition, the decomposition of benzenediazonium tetrafluoroborate with pyridine added was performed under the conditions described giving results identical with those reported.

(11) C. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press Inc., London, 1960, pp 29, 34.

(12) Calculation of the theoretical isomer distribution was done by using the percentage of *para* substitution as a measure of the extent of radical participation; *i.e.*, no yield of *para* indicates a completely cationic process (data from benzenediazonium tetrafluoroborate), whereas 36% indicates a predominantly radical process (N-nitrosoacetanilide). This approach gives the partitioning of the decomposition of benzenediazonium chloride as 43% radical and 57% cationic. Calculations of the remaining isomer percentage on this basis predicts *ortho*, 33%; *meta*, 51%; and *para*, 16%. This deviates from the observed distribution by 6%. However, this method cannot be applied to the results obtained in bromobenzene.

Chemical evidence for the intermediacy of phenyl radicals is shown by the minor iodine abstracting ability of intermediates generated in the decomposition of the diazonium chloride monohydrate[13] in the presence of *m*-chloroiodobenzene. In contrast, decomposition of the diazonium tetrafluoroborate shows no trace of abstraction product (Table V).

The variation of product composition in the decomposition of N-nitrosoacetanilide, benzenediazonium chloride, and benzenediazonium tetrafluoroborate in the presence of molecular iodine supplements the above observation. Aryl radicals, generated from N-nitrosoacetanilide react predominatly with iodine, whereas aryl cations, formed from benzenediazonium tetrafluoroborate, are insensitive to the added halogen. The intermediate(s) generated from benzenediazonium chloride give a product composition intermediate between these extremes, showing a significant fraction of reaction with iodine (Table VI).

These results are consistent with the mechanism postulated for the Gomberg reaction.[6] Reaction of amyl nitrite with aniline gives diazohydroxide which combines with itself to form the diazoanhydride ultimately decomposing to yield phenyl radicals. In the presence of strong acid, the diazohydroxide is converted into the diazochloride which then decomposes heterolytically and homolytically to give both radical and cation intermediates (Scheme I). The good agreement of data from reaction of aniline hydrochloride, benzenediazonium chloride, and the hydrated form of the diazonium salt support this scheme.

The presence of complex radical intermediates, acting as hydrogen-abstracting agents, is neither necessitated nor excluded by the available data. However, there is no evidence to suggest that such a species, similar to that recently postulated in the decomposition

(13) Diazotization of aniline hydrochloride with amyl nitrite in ether was presumed to yield the anhydrous salt. However, decomposition in benzene gave in addition to the expected products (biphenyl and chlorobenzene) phenol, diphenyl ether, the isomeric chlorobiphenyls, and *o*- and *m*-phenylphenol. (*p*-Phenylphenol was not detected under the analysis conditions.) These spurious products comprised >60% of the product composition and were identified by a correlation of gas chromatographic and mass spectral data. To measure the amount of water present, freshly prepared benzenediazonium chloride was dissolved in deuterium oxide. Decomposition takes place in solution presumably to form phenolic and azo coupling products and hydrochloric acid. Nuclear magnetic resonance analysis of the mixture shows a complex multiplet(s) centered at τ 1.77 which is attributed to the aromatic protons of the diazonium salt and any products formed in solution. There is also a sharp singlet at τ 5.41 which, in the acidic medium, can be attributed to the water, phenolic, and hydrochloric acid protons in the system. Integration of these regions gives an aromatic/"aqueous" ratio of 5.00:2.06. Since the only source of proton in the system is the diazonium salt, the integration is strong evidence for the presence of the hydrate, whose theoretical aromatic/"aqueous" ratio would be 5.00:2.00.

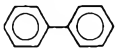
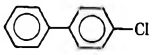
Decomposition of benzenediazonium chloride monohydrate in the solid state leads to the same products, with the exception of biphenyl, which are observed from decomposition in benzene. The product composition—phenol, 3%; chlorobenzene, 5%; diphenyl ether, 17%; chlorobiphenyls, 15%; and phenylphenols, 4%—is similar to that observed in the solution reaction. It was subsequently found that the rate of stirring of the heterogeneous benzene–diazonium ion mixture had a decided effect on the yield of these products. These observations suggest that only reaction in the solid state, prior to extraction into solution, gives rise to these aromatic materials.

This is supported by the following observations. Decomposition of benzenediazonium chloride, prepared from the reaction of phenyl isocyanate and nitrosyl chloride,[14] under the same conditions shows a marked diminution in products resulting from the reaction of phenyl cation and water. For example, the ratio of diphenyl ether to biphenyl drops from 4.0 to 1.0. (Water uptake during isolation of the salt can account for the occurrence of the products.) Moreover, these products are not observed on diazotization of aniline hydrochloride which involves *in situ* formation of the diazonium chloride.

(14) We thank Professor K. Scherer for supplying us with experimental details.

TABLE V

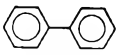
EXTENT OF IODINE ABSTRACTION BY REACTION INTERMEDIATES[a]

	% yield			
				
$(C_6H_5CO_2)_2$[b]	4.0	43	23	17
$C_6H_5N_2^+Cl^-\cdot H_2O$	41	2.4	6.2	2.0
$C_6H_5NH_3^+Cl^-$/AmONO	13	0.4	0.8	1.3
$C_6H_5N_2^+BF_4^-$		0.0		0.0

[a] Precursor/*m*-chloroiodobenzene/benzene = 1.0:1.0:16.9. [b] Data *cf.* ref. 8b.

TABLE VI

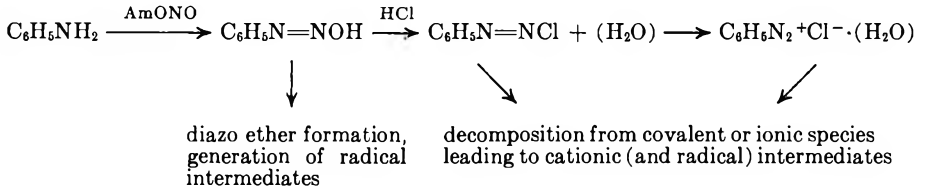
REACTION OF RADICAL AND CATION PRECURSORS WITH IODINE[a]

		Product composition, %			
					
Precursor	% yield				
$C_6H_5N(NO)COCH_3$	18.3			96.2	3.8
$C_6H_5N_2^+Cl^-\cdot H_2O$	66.2		26.2	61.0	12.8
$C_6H_5N_2^+BF_4^-$	69.6	94.1		0.1	5.8

[a] Benzene/precursor/I_2 = 30:1:0.5.

SCHEME I

EFFECT OF STRONG ACID



of N-nitrosoacetanilide,[15] plays a major function in the formation of the aryl radical.

Experimental Section

Reagents.—N. F. grade Mallinckrodt amyl nitrite was used without purification.

N-Nitrosoacetanilide was prepared from acetanilide and nitrosyl chloride according to the method of DeTar.[16]

Benzenediazonium chloride and benzenediazonium tetrafluoroborate were prepared from the appropriate aniline acid salt by diazotization with amyl nitrite in ethanol. This is a modification of the Knoevenagel preparation of diazonium ion salts.[17]

***m*-Chloroiodobenzene** was prepared *via* aqueous diazotization of *m*-chloroaniline in the presence of potassium iodide, a modification of the method of Lucas and Kennedy[18] for the preparation of iodobenzene.

Reaction Procedure.—The following general procedure was followed in carrying out reactions. Amyl nitrite (1.4 g, 0.012 mol) was added to a stirred solution of aniline (0.93 g, 0.01 mol) and 30 ml of aryl solvent in a 50-ml, round-bottom flask equipped with a reflux condenser and bubbler. The flask was then placed in an oil bath and gradually heated to reflux. When a high-boiling solvent or solvent mixture was used, reaction temperature was maintained at 120°. Reaction was allowed to continue until gas evolution ceased. The mixture was allowed to cool and an internal standard was added. Analysis was performed *via* gas–liquid partition chromatography.

The reaction of benzenediazonium chloride, aniline hydrochloride, and N-nitrosoacetanilide were carried out in the same manner, substituting the appropriate reagent for aniline. No amyl nitrite was added in the decomposition of benzenediazonium chloride.

In the series of reactions run at 78°, temperature control was maintained by performing the reactions in a double-walled reaction vessel. Benzene was heated to reflux in the outer jacket, providing a constant temperature environment.

Competition Reactions.—Relative reactivity factors were obtained by performing the reaction(s) in solvent mixtures (~30 ml) which varied in composition.

Iodine abstraction reactions were carried out following the general procedure with those reagent concentrations described by Bunnett.[8b]

Synthetic scale reactions were generally carried out in the following manner. Amyl nitrite (70 g, 0.59 mol) was added to a stirred mixture of aniline (46.5 g, 0.5 mol) and 750 ml of aromatic solvent in a 2-l., three-necked flask, fitted with a reflux condenser and gas bubbler. The reaction mixture was heated to solvent reflux or 120°, whichever temperature was lower, and maintained at that temperature until gas evolution ceased.

Larger scale reactions can be performed using this technique. However, it is advisable that the specific system be tested at the 0.1-mol level. The rate of nitrogen evolution is sensitive to the specific solvent and amine and may become violent.

The reaction flask was then fitted with a Claisen head and condenser and solvent was distilled from the reaction mixture. Stannous chloride (200 g, 1.05 mol) in 150 ml of concentrated hydrochloric acid was then added to the mixture. The flask was then heated on a steam cone overnight. This treatment was found to be effective in removing colored by-products.

The mixture was then steam distilled and the organic layer was taken up in petroleum ether (30–60°). The extracted material was then placed on a rotary evaporator to remove the solvent and the residue was vacuum distilled. Isolated yields ranged from 12 to 40% of biaryl product.

Analysis.—The products of these reactions were analyzed by gas chromatography. Compounds were identified by comparison of their retention times to those of authentic materials. In some cases further authentication was made by collecting samples *via* glpc and comparing infrared spectra and melting points.

Analyses were carried out on either a gas chromatography instrument constructed at Case Western Reserve or a Varian Hy-Fi instrument. The quarter inch columns described below were used on the former instrument; the eighth inch columns were used on the latter.

Column A was a 5 ft × 0.25 in. copper column packed with G.E.-SF-96 (20%) on Chromosorb P operated at 210° with a

(15) G. R. Chalfont and M. J. Perkins, *J. Amer. Chem. Soc.*, **89**, 3054 (1967).

(16) D. F. DeTar, *ibid.*, **73**, 1448 (1951).

(17) E. Knoevenagel, *Ber.*, **23**, 2995 (1890).

(18) H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 351.

He inlet pressure of 32 psi. Column B was a 7 ft × 0.125 in. stainless steel column packed with Apiezon L (15%) on Chromosorb W operated at 210° with a N_2 inlet pressure of 15 psi. Column C was a 5 ft × 0.125 in. stainless steel column packed with SE-30 (5%) on Chromosorb W operated at 167° with a N_2 inlet pressure of 15 psi. Column D was a 10 ft × 0.25 in. copper column packed with Apiezon L (25%) on Chromosorb W operated at 195° with a He inlet pressure of 40 psi.

Determination of product yields was made by comparing peak areas with that of an internal standard. Adjustment was made for differences in thermal conductivity and applied to correct the observed areas.

Notes

Aprotic Diazotization of Aniline in the Presence of Iodine[1,2]

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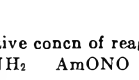
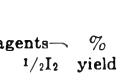
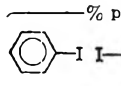
The reaction of arylamines with amyl nitrite in aromatic solvents has been conclusively demonstrated to generate aryl radicals.[4] The presence of a radical intermediate in this reaction suggested the use of iodine, which might serve as the radical trap,[5] to give a facile method for the formation of aryl iodides. When aniline was treated with amyl nitrite in benzene in the presence of an equivalent of iodine,[6] iodobenzene was formed in 50% yield with small amounts of biphenyl. However, in addition to the expected products, a significant amount of *p*-diiodobenzene was found.[7]

To investigate the source of the diiodinated product, the relative amounts of aniline, iodine, and amyl nitrite were varied (Table I). When aniline is present in excess relative to amyl nitrite, the product composition is insensitive to excess iodine. When amyl nitrite is in excess the expected increase in diiodinated product with increasing iodine concentration is observed. Biphenyl formation does not become significant until less than an equivalent of iodine is present. Iodine acts as a more effective radical trap than benzene by a factor of $\sim 2 \times 10^3$.

These results do not, however, uncover the source of *p*-diiodobenzene. Addition of iodobenzene to an aprotic diazotization reaction had no effect on the yield of diiodinated product. Diazotization of aniline hydroiodide and decomposition of N-nitrosoacetanilide and benzenediazonium chloride under conditions similar to those employed in the reaction system gave no *p*-diiodobenzene (Table II). Since these compounds are analogous to either suggested intermediates or transient oxidation states in the diazotization sequence, the iodination process must occur prior to the diazotization reaction. Thus, *p*-iodoaniline is postulated as the precursor of *p*-diiodobenzene. When the isomeric iodoanilines are diazotized under reaction conditions, high yields of the respective diiodobenzenes are formed without side products within the limits of detection (glpc). Isolation of *p*-iodoaniline from reactions where an excess of aniline relative to amyl nitrite was employed conclusively demonstrates the intermediacy of this species as precursor of *p*-diiodobenzene.

TABLE I
PRODUCT COMPOSITION AS A FUNCTION OF REAGENT RATIOS

Relative concn of reagents			%	% product compn		
$C_6H_5NH_2$	AmONO	$^1/_2I_2$	yield			
2	1	2	56	89	10	1
2	1	1	47	86	11	3
1	1	1	60	78	21	1
1	3	1	77	85	13	2
1	1.2	3	63	57	39	4
1	1.2	2	60	64	33	3
1	1.2	1	60	82	16	2
1	1.2	0.7	38	77	14	9
1	1.2	0.5	41	77	2	21

The direct reaction of aniline and molecular iodine cannot account for the formation of *p*-iodoaniline in this system. When an aniline–benzene mixture was refluxed for 3 hr with an equivalent amount of iodine, iodination of aniline did occur. However, the yield was low, and a mixture of isomers (20% *ortho*, 80% *para*) was obtained. This is not consistent with the relatively high yields and isomer distribution of diiodobenzenes (*ortho* <1%, *para* >99%) obtained from the diazotization reaction. Iodination of aniline in aqueous bicarbonate solution,[8] involving hypoiodous acid as the iodinating agent,[9] gives almost exclusively the *para* isomer (4% *ortho*) in high yield. Other examples of electrophilic iodination have also shown great *para* selectivity.[10,11] Thus, a cationic species is postulated as the iodinating agent in this system. An attractive mechanism for the generation of such a species is the oxidation of iodine by alkoxyl or hydroxyl radical. These oxidizing agents are generated in the diazotization process and could react with iodine to

(1) Aprotic refers to solvents that are not proton donors. Other examples of such diazotizations are summarized by D. Y. Curtin, J. A. Kampmeier, and B. R. O'Connor, *J. Amer. Chem. Soc.*, **87**, 863 (1965).

(2) Financial support (Grant No. GP 3976) from the National Science Foundation is gratefully acknowledged.

(3) National Science Foundation Graduate Trainee.

(4) L. Friedman and J. F. Chlebowski, *J. Org. Chem.*, **33**, 1633 (1968).

(5) G. S. Hammond, *J. Amer. Chem. Soc.*, **72**, 3737 (1950).

(6) 1 equiv of iodine = $^1/_2I_2$ (127 g).

(7) Small (<1%) amounts of *o*-diiodobenzene were also detected.

(8) R. Q. Brewster, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p 347.

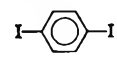
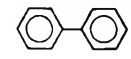
(9) R. M. Hann and J. Berliner, *J. Amer. Chem. Soc.*, **47**, 1710 (1925).

(10) O. Orazi, R. Corral, and H. Bertello, *J. Org. Chem.*, **29**, 1101 (1964).

(11) E. Berliner, *J. Amer. Chem. Soc.*, **72**, 4003 (1950).

TABLE II

PRODUCTS FROM THE REACTION OF POSSIBLE PRECURSORS OF *p*-DIIODOBENZENE WITH IODINE

Precursor[a]	% yield	% product compn			
					
$C_6H_5N(NO)COCH_3$	18.3		96.2	0.0	3.8
$C_6H_5N_2{}^+Cl^-/H_2O$	66.2	26.2	61.0	0.0	12.8
$C_6H_5NH_3{}^+I^-/AmONO$[b]	64.0		97.6	0.0	2.3
p-$IC_6H_4NH_2/AmONO$	63.9		0.0	100.0	0.0

[a] In the presence of $^1/_2I_2$ in excess benzene. [b] No I_2 present.

TABLE III

APROTIC DIAZOTIZATION OF AROMATIC AMINES WITH IODINE PRESENT[a]

R of $RC_6H_4NH_2$	Solvent	% yield	% product compn				
			RC_6H_4I	RC_6H_5	RC_6H_4Cl	$RC_6H_4C_6H_5$	$RC_6H_3I_2$
H	CCl_4	60.7	81	0	4		15[b]
H	C_6H_6	58.4	84			2	14[b]
m-CH_3	CCl_4	19.7	43	Trace	20		37[c]
m-CH_3	C_6H_6	49.5	74	3		2	21[c]
p-CH_3	CCl_4	48.6	83	1	5		11[d]
p-CH_3	C_6H_6	59.8	93	1		0	6[d]
p-I	CCl_4	49.8	80	6	14		0
p-I	C_6H_6	63.9	100	0		0	0

[a] $RC_6H_4NH_2/AmONO/^1/_2I_2$ = 1:1.2:1. [b] p-Diiodobenzene. [c] Mixture of 2,3- and 2,5-diiodotoluene. [d] 2,4-Diiodotoluene.

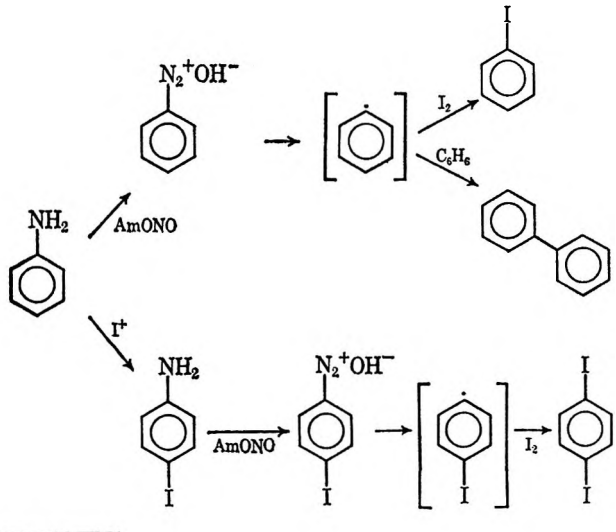
give alkyl hypoiodite or hypoiodous acid. Alternative and/or additional processes are possible.[12]

Iodobenzene may also be formed by hydrogen abstraction by *p*-iodophenyl radical. However, the reaction of aniline, *m*-toluidine, and *p*-iodoaniline with amyl nitrite and iodine in benzene or carbon tetrachloride yielded only small amounts of reduction product (Table III). At best, less than 1% of the iodobenzene formed can be accounted for by this scheme.

The above results are consistent with Scheme I. Amyl nitrite and an electrophilic iodinating agent compete for available aniline. The first process, a relatively fast reaction, ultimately gives phenyl radical which can react further with either iodine or benzene to form either iodobenzene or biphenyl, respectively.[13] Reaction of aniline with the iodinating agent, the generation of which may be dependent on the reaction of aniline and amyl nitrite, is a relatively slow process. *p*-Iodoaniline, generated *in situ* from this reaction undergoes diazotization with amyl nitrite to then yield *p*-iodophenyl radical. *p*-Diiodobenzene is formed on reaction of this species with iodine.[14]

The use of this reaction in the preparation of aryl iodides is only slightly limited by the competing side reaction. The desired product, obtainable in a 50% yield, can be easily separated from other materials by steam or vacuum distillation. In addition, the reaction of the iodoanilines and toluidines suggests that substituted amines may not be subject to this complication. The facility with which the reaction is accomplished indicates that it is an attractive alternative to the classical aqueous diazotization method.[15]

SCHEME I



(12) Refluxing equivalent amounts of amyl nitrite and iodine in excess benzene produces no iodobenzene. With an equivalent of acetic acid added to this system, only trace (<0.5%) amounts of iodobenzene were detected. No product formation occurred when sodium nitrite was substituted for the alkyl nitrite. Thus, generation of an iodinating agent by reaction of iodine with amyl nitrite does not occur.

(13) An additional source of iodobenzene can be aniline hydroiodide formed *in situ* as a reaction by-product. On reaction with amyl nitrite, this material yields iodobenzene almost exclusively (Table II).

(14) *p*-Iodobiphenyl is not observed. If the competition for *p*-iodophenyl radical between benzene and iodine is similar to that observed for phenyl radical, only trace amounts of *p*-iodobiphenyl would be formed and would not be detected with the analytical method used.

(15) H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 143, p 351.

(16) D. F. DeTar, *J. Amer. Chem. Soc.*, **73**, 1448 (1951).

(17) E. Knoevenagel, *Ber.*, **23**, 2995 (1890).

Experimental Section

Reagents.—N. F. grade Mallinckrodt "amyl" (isopentyl) nitrite was used without purification.

N-Nitrosoacetanilide was prepared from acetanilide and nitrosyl chloride using the method described by DeTar.[16]

Benzenediazonium chloride hydrate was prepared from aniline hydrochloride by diazotization with amyl nitrite in ethanol. This is a modification of the Knoevenagel preparation of diazonium ion salts.[17]

Procedure.—Reactions were carried out in the following manner. Amyl nitrite (1.4 g, 0.012 mol) was added to a stirred mixture of aniline (0.93 g, 0.01 mol), iodine (1.26 g, 0.005 mol), and 30 ml of benzene (or other aromatic solvent) in a 50-ml, round-bottom flask equipped with a reflux condensor and gas

bubbler. The flask was then placed in an oil bath and gradually heated to solvent reflux. The temperature of the oil bath was maintained at 100°. Reaction was allowed to continue until gas evolution ceased. The mixture was then allowed to cool to room temperature, internal standard was added, and analysis was performed.

Analysis.—The products of these reactions were analyzed by gas chromatography. Compounds were identified by comparison of their retention times to those of authentic materials. In some cases further authentication was made by collecting samples *via* glpc and comparing the infrared spectra and melting points.

Analyses were carried out on a gas chromatography instrument constructed at Case Western Reserve equipped with a 5 ft × 0.25 in. copper column packed with GE-SF-96 (20%) on Chromosorb P operated at 210° with a He inlet pressure of 32 psi.

Determination of product yields was made by comparing peak areas with that of an internal standard, *p*-chlorobiphenyl, adjusting for molar thermal conductivity difference.

Synthetic Application.—*p*-Iodotoluene was prepared in 40% yield by a modification of the procedure described above. Iodine (150 g, 1.18 equiv) and amyl nitrite (140 g, 1.2 mol) were added to 1 l. of benzene in a 2-l., three-necked flask equipped with a mechanical stirrer and reflux condensor. *p*-Toluidine (107 g, 1.0 mol), dissolved in ~200 ml of benzene, was added dropwise over a 2-hr period. The reaction is sufficiently exothermic to bring the solution to reflux temperature without external heating; caution must be exercised in the rate of addition. The rate of nitrogen evolution is dependent on the amine and is accelerated in the presence of iodine and may become excessively vigorous. After allowing the reaction to reflux for an additional 2 hr, the mixture was washed with 700-ml portions of 5% sodium bisulfite solution, water, 5% potassium hydroxide solution, and water. Solvent was removed on a rotary evaporator and the remainder was steam distilled. The organic layer was extracted with petroleum ether (30–60°) and distilled under a vacuum to yield white plates, mp 34–35° (lit.[18] mp 35°), in 40% yield of >99% purity (glpc).

(18) A. Edinger and P. Goldberg, *Ann.*, **157**, 347 (1871).

The Syntheses of Substituted Imidazo[1,2-*a*]pyridines *via* "Ylidelike" Intermediates

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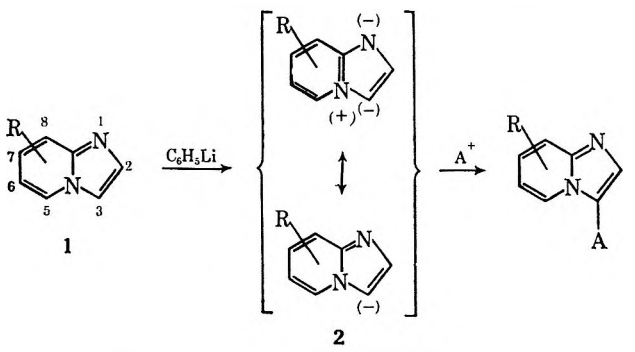
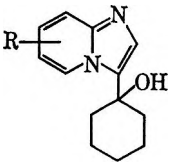
We have recently described the base-catalyzed protium–deuterium exchanges that occur in various "polyazaindenes."[1,2] The application of these observations to the syntheses of substituted imidazo[1,2-*a*]pyridines is outlined by the reaction sequence[3,4]



1 2

(1) W. W. Paudler and L. S. Helmick, *Chem. Comm.*, 377 (1967).
(2) W. W. Paudler and L. S. Helmick, *J. Org. Chem.*, **33**, 1087 (1968).

We now wish to report the syntheses of a number of substituted imidazo[1,2-*a*]pyridines by this method. The substances prepared by addition of cyclohexanone to compound **2** are represented by the general structure given for compounds **4–8**. The addition of dimethyl-

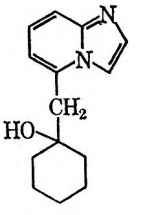


4, R = H
5, R = 6-CH_3
6, R = 7-CH_3
7, R = 8-CH_3
8, R = 2-CH_3

formamide and phenyl isocyanate to compound **2** (R = H) affords the imidazo[1,2-*a*]pyridine-3-carboxaldehyde and -3-carboxanilide, respectively. The structure proofs of the various compounds rest upon their nmr (see Table I) and mass (see Experimental Section) spectra and the usual elemental analyses.

The considerable deshielding effect that the substituent in the three position has upon H_5 is of some interest and also contributes considerably to the structure elucidation of these compounds.

A further point of interest is the observation that the protons of the 5-methyl group are the only protons of the various isomeric methylimidazo[1,2-*a*]pyridines that are sufficiently acidic to react with phenyllithium to yield, after treatment with cyclohexanone, compound **11**.



11

The structure proof of this compound rests upon its nmr spectrum (the absence of a methyl group) and the other identifying features reported in the Experimental Section. 3-Methylimidazo[1,2-*a*]pyridine could, potentially, afford a substance analogous to **11**. However, under the reaction conditions which give the products reported in this Note, *no reaction* occurs between phenyllithium and the 3-methyl compound, the latter being recovered from the reaction mixture. The reactivity of the 5-methyl group is reminiscent of that of the 2-methyl group in pyridines.[5]

Experimental Section[6]

(1-Hydroxycyclohexyl)imidazo[1,2-*a*]pyridines.—To a stirred solution of 2.6 mmol of the appropriate imidazo[1,2-*a*]pyridine

(3) During the course of this work, the reaction of pyridine N-oxides, under similar reaction conditions, with cyclohexanone was described and interpreted in terms of an ylide intermediate: R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967).

(4) A. W. Johnson ["Ylid Chemistry in Organic Chemistry, A series of monographs," Vol. 7, A. T. Blomquist, Ed., Academic Press Inc., New York, N. Y., 1966, suggests the use of the term "ylid" rather than "ylide."

(5) "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955: R. B. Woodward and E. C. Kornfeld, p 413; L. A. Walter, p 757, and elsewhere.

(6) Melting points are corrected. The nmr spectra were obtained with a Varian A-60 spectrometer and the mass spectra were determined with a Hitachi Perkin-Elmer RMU-6E mass spectrometer.

TABLE I

NMR SPECTRAL DATA OF SOME SUBSTITUTED IMIDAZO[1,2-*a*]PYRIDINES[a]

Compd	Chemical shifts, τ						Substituents[d,e]
	H_2	H_3	H_5	H_6	H_7	H_8	
4[c]	2.69		1.22	3.23	2.88	2.53	
5[b]	2.92		1.56		3.12	2.72	7.76 (CH_3—)
6[c]	2.76		1.32	3.32		2.77	7.68 (CH_3—)
7[b]	3.10		1.42	3.36	3.18		7.52 (CH_3—)
8[b,g]			0.60	2.18[f]	2.63	2.18[f]	7 30 (CH_3—)
9[b]	1.67		0.40	2.89	2.45	2.19	0.05 (—CHO)
10[b]	1.64		0.42	(2.82)	(2.70)	(2.64)	−0.01 (>NH), 2.80 phenyl protons (multiplet)
11[c]	2.50	1.98		3.30	2.82	2.58	6.92 (—CH_2—)

[a] The spin–spin coupling constants of the heterocyclic ring protons are essentially the same as those reported for similar compounds (see ref 1 and 2 and references cited therein). Figures in parentheses indicate approximate chemical shifts only because of interference with other protons. [b] Dilute solutions in $CDCl_3$. [c] Dilute solutions in DMSO-d_6. [d] The chemical shifts of the hydroxyl protons (τ 4.92–6.82) are not listed for each compound. [e] A complex ten-proton multiplet due to the cyclohexyl protons occurs at approximately τ 8.25 ± 0.1 for compounds **4**–**8** and **11**. [f] Center of a complex two-proton multiplet due to H_6 and H_8. [g] In CF_3CO_2D.

TABLE II

ANALYTICAL DATA FOR VARIOUS (1-HYDROXYCYCLOHEXYL)IMIDAZO[1,2-*a*]PYRIDINES

Compd	Mp, °C	Formula	Analyses, %						Mol wt (mass spectroscopy)	Yield, %
			Calcd			Found				
			C	H	N	C	H	N		
4	189–192	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	71.89	7.45	13.06	216	35
5	173–175	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	73.15	7.83	12.44	230	40
6	201–203	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	72.93	7.87	12.31	230	48
7	209–210	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	73.22	7.90	12.31	230	42
8	215–217	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	73.13	8.26	12.20	230	14
11	156–157	$C_{14}H_{18}N_2O$	73.01	7.88	12.17	73.22	7.83	12.47	230	35

in 10 ml of anhydrous ether was added dropwise, under a deoxygenated and dried nitrogen atmosphere, 1.5 ml of a 2.14 *M* solution of phenyllithium in a 70 : 30 mixture of benzene–ether (purchased from Alfa Inorganics, Inc., Beverly, Mass.). The brown to dark pink reaction mixture was stirred for 10 min (extension of the stirring time did not affect the yield of the product) and treated with 3 mmol of cyclohexanone in 10 ml of anhydrous ether. The color of the mixture changed gradually to a yellow-orange. After 30 min, the reaction mixture was treated with water and the organic layer was separated and extracted with 5% aqueous HCl. The aqueous layer then exhaustively extracted with chloroform and washed with 5% HCl. The combined acid solution was washed with chloroform and basified with solid sodium carbonate to precipitate a solid product (for 8-methylimidazo[1,2-*a*]pyridine) or oil, that was extracted with chloroform. The extract was dried over anhydrous sodium sulfate, concentrated under reduced pressure, and chromatographed on alumina (activity III). Elution with chloroform gave the solid product that was purified by recrystallization from dilute ethanol or by sublimation. The analytical and physical data are given in Table II.

3-Formylimidazo[1,2-*a*]pyridine. **A.**—A solution of 660 mg (5.6 mmol) of imidazo[1,2-*a*]pyridine in 25 ml of anhydrous ether was treated with 3 ml of the phenyllithium solution according to the above procedure and with 400 mg of N,N-dimethylformamide in 10 ml of anhydrous ether. The brown reaction mixture was stirred until an orange mixture resulted (*ca.* 1 hr) and water was added. The aqueous layer was exhaustively extracted with ether, and the combined ether layers were dried over anhydrous sulfate and concentrated under reduced pressure to give a yellow oily solid. The $CHCl_3$-soluble portion of the product was chromatographed on alumina (activity III). Elution with chloroform afforded 200 mg (24%) of product (mp 117–119°). The product was crystallized from ligroin (bp 95–105°) and sublimed [70° (0.4 mm)] to yield colorless needles: mp 117–119°; pmr ($CDCl_3$), CHO at τ 0.05.

Anal. Calcd for $C_8H_6N_2O \cdot H_2O$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.60; H, 4.68; N, 16.72; mol wt (mass spectroscopy), 146.

The semicarbazone was found to have mp 265° dec.

Anal. Calcd for $C_9H_9N_5O$: C, 53.19; H, 4.46; N, 34.47. Found: C, 53.09; H, 4.45; N, 34.04.

B.—The reaction was also carried out by a reversed addition procedure (addition of the imidazo[1,2-*a*]pyridine solution into the phenyllithium solution) to obtain the aldehyde **9** in 17% yield. A reaction at ice bath temperature gave unreacted starting material.

C.—Procedure B was carried out at room temperature by using 0.01 mol of imidazo[1,2-*a*]pyridine, 8 ml of a *ca.* 1.6 *M* butyllithium solution in hexane (purchased from Foote Mineral Co., Exton, Pa.), and 0.8 g of N,N-dimethylformamide in 16 ml of anhydrous ether to give the aldehyde **9** in 30% yield.

3-Imidazo[1,2-*a*]pyridinecarboxyanilide (10).—Procedure B was adapted by using 1.18 g (0.01 mol) of imidazo[1,2-*a*]pyridine in 15 ml of anhydrous ether, 8 ml of the phenyllithium solution diluted with 10 ml of anhydrous ether, and a solution of 1.2 g of phenyl isocyanate in 15 ml of anhydrous ether. The green reaction mixture was stirred for 30 min, treated with 10 ml of absolute ethanol,[7] stirred for 30 min, and treated with water. The organic layer was extracted with 5% HCl. Basification of the acid solution with solid sodium carbonate gave a yellow precipitate that crystallized from ethanol to yield 250 mg (15%) of colorless needles: mp 225°; pmr (DMSO-d_6), NH at τ − 0.01.

Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.62; H, 4.54; N, 17.73; mol wt (mass spectroscopy) 237.

Chloroform extraction of the aqueous layer separated from the reaction mixture, followed by acid–base extraction and chromatography on alumina eluting with chloroform, gave 0.87 g of the starting material.

Registry No.—**4**, 15833-18-8; **5**, 15833-19-9; **6**, 15833-20-2; **7**, 15833-23-5; **8**, 15833-24-6; **9**, 6188-43-8; **9** semicarbazone, 15833-21-3; **10**, 15833-22-4; **11**, 15856-41-4.

(7) D. A. Shirley and P. A. Roussel, *J. Amer. Chem. Soc.*, **75**, 375 (1953).

Products Obtained from the Reaction of Molecular Oxygen with the Sodium Salts of 3-Phenyloxindoles and 3-Phenyl-2-cumaranone

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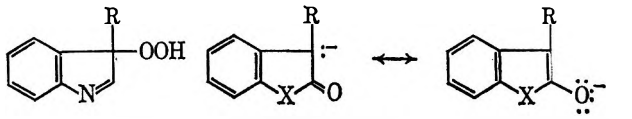
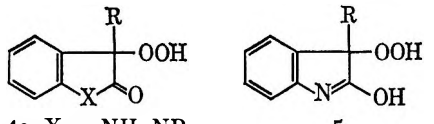
The reaction of molecular oxygen with indoles and compounds containing an indole nucleus to form 3-hydroxyperoxyindolenines such as **1** has been described in the literature.[1] Under the proper conditions the 3-phenyl derivatives of **1** (R = aryl) can be converted into the pharmaceutically useful 2-aminobenzophenones as with **2a**.[2]



1 **2a**, X = NH, NR_1; **b**, X = O **3a**, X = NH, NR_1; **b**, X = O

The 3-carbanion of an oxindole (**2a**), which can also be represented as the oxy anion of a 2-hydroxyindole (**3a**), might also be expected to react with oxygen to form a hydroperoxide **4a** or **5**. When R is an aryl



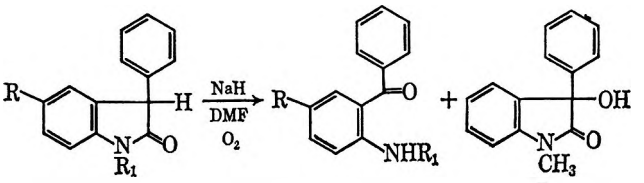
4a, X = NH, NR_1; **b**, X = O **5**

group it should also be possible to convert **4a** or **5** into 2-aminobenzophenones. In a similar way the carbanion of a 2-cumaranone (**2b** or **3b**) can form a hydroperoxide (**4b**) that can be converted into a 2-hydroxybenzophenone when R in **4b** is phenyl.

Several examples of the reaction of oxygen with alkaline solutions of oxindoles have been reported. From 1,3-dimethyloxindole,[3a] 1,3-dimethyl-5-methoxyoxindole,[3b] 3-(2-aminoethyl)-oxindole,[3c] and 3-oxindole propionic acid[3d] there was obtained the corresponding dioxindole analogs. Nothing has been reported on the reaction of 2-cumaranones with oxygen.

In the present paper we wish to report our findings on the air oxidation of the anions obtained from some 3-phenyloxindoles and 3-phenyl-2-cumaranone.

The sodium salt of 3-phenyloxindole (**6a**), generated by treating a dimethylformamide solution of **6a** with sodium hydride dispersion, was gassed with a stream of air for 52 hr. After processing the reaction there was obtained a 77% yield of 2-aminobenzophenone (**7a**). In a similar manner 3-phenyl-5-chloro- (**6b**) and 3-phenyl-5-methoxyoxindole (**6c**) gave 79% and 68% yields of 2-amino-5-chloro (**7b**) and 2-amino-5-methoxybenzophenone (**7c**). When the salt of 1-methyl-3-phenyloxindole (**6d**) was oxygenated there was obtained 7% of 2-methylaminobenzophenone (**7d**) and in addition a 71% yield of 1-methyl-3-phenyldioxindole (**8**).

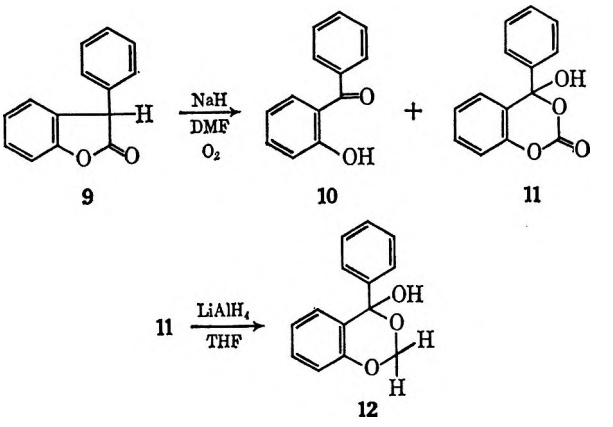


6a, R = H; R_1 = H **b**, R = Cl; R_1 = H **c**, R = OCH_3; R_1 = H **d**, R = H; R_1 = CH

7a, R = H; R_1 = H **b**, R = Cl; R_1 = H **c**, R = OCH_3; R_1 = H **d**, R = H; R_1 = CH_3

8

Treatment of a dimethylformide solution of the sodium salt of 3-phenyl-2-cumaranone (**9**) with air for 56 hr gave 5% of 2-hydroxybenzophenone (**10**) and 52% of an acidic $C_{14}H_{10}O_4$ compound. The infrared spectrum gave strong absorption in the 3.20–4.10-μ region typical of a carboxyl group, but a strong band at 5.80 μ suggested that a lactone or ester carbonyl was present.[4] The ultraviolet spectrum was typical of an isolated benzene system and the nmr spectrum disclosed one exchangeable and nine aromatic protons. Mass spectrum confirmed the empirical formula (M = 242) and also gave strong peaks at M − 45 and *m/e* 105 suggesting that a $-CO_2H$ and C_6H_5CO- might be present.



9 **10** **11**

12

Lithium aluminum hydride reduction of this compound in refluxing tetrahydrofuran gave a new weak acid with empirical formula $C_{14}H_{12}O_3$. The infrared spectrum of this substance disclosed -OH absorption at 2.92 μ but lacked any bands in the carbonyl region. The nmr spectrum disclosed one exchangeable proton, a broad two-proton singlet at 3.92 ppm, and nine aromatic protons. From the mass spectrum strong peaks at M − 31 (M = 228) and *m/e* 105 suggested the presence of a $-CH_2OH$ and C_6H_5CO- grouping.

The infrared, ultraviolet, and nmr data indicate that the $C_{14}H_{10}O_4$ compound is 4-phenyl-1,3-benzodioxan-4-ol-2-one (**11**) and the reduction product is 4-phenyl-

(1) A. G. Davies, "Organic Peroxides," Butterworth and Co. Ltd., London, 1961, pp 27–31; B. Witkop, *J. Amer. Chem. Soc.*, **72**, 1428 (1950); B. Witkop and J. B. Patrick, *ibid.*, **73**, 2196 (1951); **74**, 3855 (1952); R. J. S. Beer, T. Donavanik, and A. Robertson, *J. Chem. Soc.*, 4139 (1954); F. Ying-Hsiueh Chen and E. Leete, *Tetrahedron Lett.*, 2013 (1963); H. H. Wasserman and M. B. Floyd, *ibid.*, 2009 (1963).

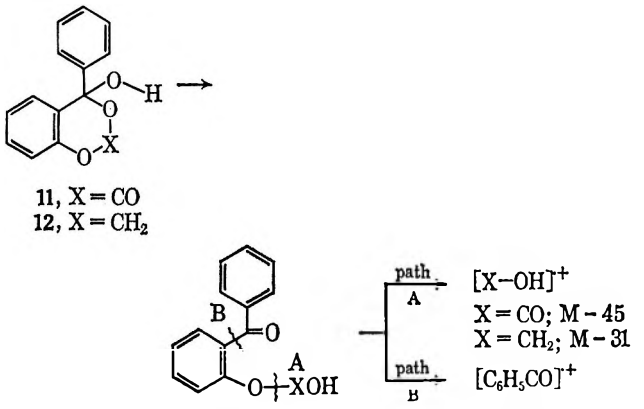
(2) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964); L. H. Sternbach, L. O. Randall, and S. R. Gustafson in "Psychopharmacological Agents," M. Gordon, Ed., Academic Press Inc., New York, N. Y., 1964, Chapter 5.

(3) (a) P. C. Julian and J. Pikl, *J. Amer. Chem. Soc.*, **57**, 539 (1935); (b) R. B. Longmore and B. Robinson, *Collect. Czech. Chem. Comm.*, **32**, 2184 (1967); (c) K. Freter, H. Weissbach, B. Redfield, S. Udenfriend, and B. Witkop, *J. Amer. Chem. Soc.*, **80**, 983 (1958); (d) E. C. Kendall and A. Osterberg, *ibid.*, **49**, 2047 (1927).

(4) L. J. Bellamy, "Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958.

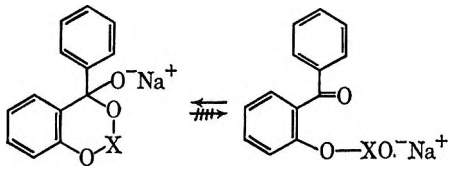
1,3-benzodioxan-4-ol (12). Additional support for these structures was obtained by hydrolyzing 11 and 12 with aqueous acetic acid. In both cases 2-hydroxybenzophenone (10) was obtained.

The apparent presence of a -COOH, $-CH_2OH$, and C_6H_5CO- groups in the mass spectrum of 11 and 12 can be explained by a thermal or electronic rearrangement of these to 11a and 12a in the mass spectrometer. Fragmentation by path A can account for the -COOH and $-CH_2OH$ groups while path B produces the C_6H_5CO- group.



11a, X = CO
12a, X = CH_2

Since the structures 11–11a and 12–12a are related to each other as ring–chain tautomers it was of interest to determine if the anions of the parent acids 11 and 12 exist in the ring (13a,b) or the chain (14a,b) forms. The gross features of the ultraviolet spectra of 11 and 12 in ethanol and sodium hydroxide–ethanol solution were identical. The position and intensity of the band maxima were typical of an isolated benzenoid chromophore rather than that of the benzophenone systems 14a and b. This establishes that in solution both the



13a, X = CO
b, X = CH_2

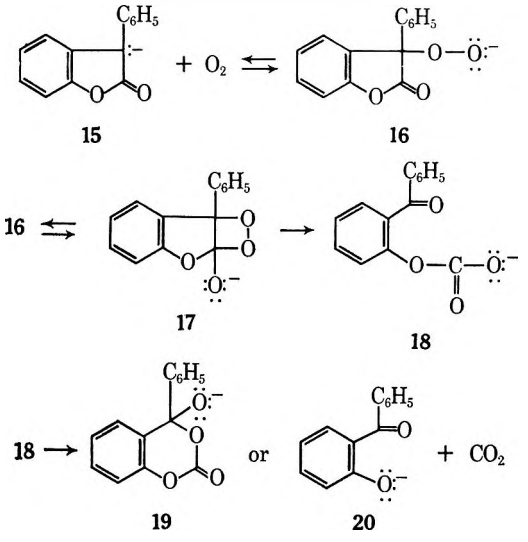
14a, X = CO
b, X = CH_2

anion and free acid exist in the ring forms 13a and b. The stability of these anions in the ring form may account for the unusual lithium aluminum hydride reduction of 11 to 12 where both C–O bonds of the starting lactone group are left intact.[5]

Although no detailed study on the mechanism of formation of the novel ring system 11 has been carried out, it seems possible to comment on this based on the analogy with the known mechanism[1] of indole anion oxidation.

Reaction of the 3-phenyl-2-cumaranone anion 15 with molecular oxygen in a manner similar to that reported[6] for other anions can give the hydroperoxide anion 16. Intramolecular attack of the negatively charged oxygen on the adjacent carbonyl carbon results in the cyclic peroxy anion 17. Bond reorganization of 17 gives the oxo carboxylate anion 18 which can react with the benzophenone carbonyl to form the cyclic anion 19 or lose carbon dioxide to give the 2-hydroxybenzophenone anion 20 (see Scheme I).

SCHEME I
MECHANISM OF OXYGEN REACTION WITH THE 3-PHENYL-2-CUMARANONE ANION



Experimental Section[7]

Synthesis of N-Aryl-DL-mandelamides.—A mixture of 15.2 g (0.10 mol) of DL-mandelic acid, 9.3 g (0.10 mol) of aniline, and 250 ml of technical *o*-dichlorobenzene were stirred and refluxed in a flask equipped with an extractor for removing water. After all the water had been removed the reaction mixture was cooled in an icebath. The resultant solid was filtered off and crystallized from methanol–water to give 15.1 g (66%) of N-phenyl-DL-mandelamide: mp 146–147° (lit.[8a] mp 148°); ir (KBr), 3.04 and 3.08 (NH, OH), and 6.01 μ (C=O).

In a similar manner 152 g (1.0 mol) of DL-mandelic acid, 127.6 g (1.0 mol) of *p*-chloroaniline, and 2000 ml of technical *o*-dichlorobenzene gave 176 g (67%) of N-*p*-chlorophenyl-DL-mandelamide: mp 160–163° (CH_3OH–H_2O); ir (KBr), 3.01 and 3.09 (NH, OH) and 6.00 μ (C=O).

Anal. Calcd for $C_{14}H_{12}ClNO_2$: C, 64.3; H, 4.6; Cl, 13.4; N, 5.4; O, 12.3. Found: C, 64.0; H, 4.5; N, 5.5.

From 152 g (1.0 mol) of DL-mandelic acid, 123 g (1.0 mol) of *p*-methoxyaniline, and 2000 ml of technical *o*-dichlorobenzene there was obtained 206 g (80%) of N-*p*-methoxyphenyl-DL-mandelamide: mp 148–150° (CH_3OH–H_2O); ir (KBr), 3.03 and 3.07 (NH, OH) and 6.02 μ (C=O).

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.0; H, 5.8; N, 5.4; O, 18.8. Found: C, 69.9; H, 5.7; N, 5.5.

Cyclization of N-Aryl-DL-mandelamides to 3-Aryloxindoles. 3-Phenyloxindole (6a).—Following the procedure of Bruce and Sutcliffe[8a] there was obtained 2.5 g of crude 3-phenyloxindole (6a) from 5.7 g of DL-N-phenylmandelamide. Vacuum sublimation (0.5 mm) at 120–130° gave 1.78 g of pure 6a, mp 186–189° (lit. mp 191°[8a] and 185–187°[8b]).

(5) A survey of the literature failed to uncover any example where a carbonate, cyclic or open chain, has been reduced with lithium aluminum hydride or other reducing hydride. By analogy with the hydride reduction of esters and lactone the carbonates would be expected to reduce to alcohols.

(6) H. R. Gersmann, H. J. W. Nieuwenhuis, and A. F. Bickel, *Tetrahedron Lett.*, 1383 (1963).

(7) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and have not been corrected. Proton nmr spectra were obtained on a Varian Associates A-60 spectrometer and are recorded in parts per million (ppm) from an internal tetramethylsilane standard. Infrared spectra were determined on a Perkin-Elmer Infracord. Ultraviolet spectra were carried out on a Cary Model 15 spectrometer. Potentiometric titrations were run on a Metrohm recording potentiometric titrator Model E 336. Mass spectra were determined on a Consolidated Electronics Co. mass spectrometer Model 21 103C, equipped with an all-glass heated inlet. Samples were injected by the direct inlet technique at a source temperature of approximately 250°.

(8) (a) J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 4793 (1957); (b) C. Marschalk, *Bull. Soc. Chim. Fr.*, 949 (1952).

3-Phenyl-5-chloroxindole (6b).—To a cold, rapidly stirred mixture of 225 ml of concentrated sulfuric acid (96%) and 25 ml of fuming sulfuric acid (65% oleum) there was added portionwise 50 g of DL-N-*p*-chlorophenylmandelamide. The internal temperature was not allowed to exceed 40° during this addition. The mixture was stirred an additional 1.5 hr at room temperature and then poured onto 1000 g of crushed ice. The solid was filtered off and crystallized from CH_3OH–H_2O (1:1) to give 43.5 g of crude 6b, mp 185–187°. Vacuum sublimation (0.5 mm) of this material at 150–160° gave 35.4 g of 3-phenyl-5-choroxindole (6b): mp 191–193°; ir (KBr), 3.00 (NH) and 5.89 μ (C=O).

Anal. Calcd for $C_{14}H_{10}ClNO$: C, 69.0; H, 4.1; Cl, 14.5; N, 5.7; O, 6.6. Found: C, 68.8; H, 3.9; Cl, 14.6; N, 5.8; O, 6.6.

3-Phenyl-5-methoxyoxindole (6c).—A mixture of polyphosphoric acid (60 g) and DL-N-*p*-methoxyphenylmandelamide (5.0 g) were stirred and heated at 50° for 1.5 hr. The viscous product was then poured into ice water and extracted three times with chloroform. The chloroform was washed with saturated sodium chloride and dried with magnesium sulfate. Removal of the chloroform gave 5.0 g of crude product, mp 80–170°. Chromatography of this material on a silica gel column ($CHCl_3$–C_6H_6, 1:1, eluent) gave 1.7 g of 3-phenyl-5-methoxyoxindole (6c): mp 195–197° (CH_3OH–H_2O); ir (KBr), 3.01 (NH) and 5.91 μ (C=O).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.4; N, 5.9. Found: C, 75.0; H, 5.2; N, 5.9.

An attempt to prepare 6c by the sulfuric acid technique given above failed to give any water-insoluble material.

N-Methyl-3-phenyloxindole (6d).—N-Methyl-3-phenyloxindole was prepared by the aluminum chloride cyclization of N-methyl-α-bromophenylacetanilide. It had mp 120° (lit.[8a] mp 119.5°); ir (KBr), 5.86 (C=O), 6.18, 6.67, 6.81, 7.26, and 7.43 μ; uv, λ_{max}^{EtOH} 249 mμ (ϵ 8030).

Air Oxidation of the Sodium Salts of 3-Phenyloxindoles. A. 3-Phenyloxindole (6a).—To a flask equipped with a magnetic stirring bar, gas inlet tube, and a calcium chloride drying tube there was added 2.5 g (0.012 mol) of 3-phenyloxindole, 1.5 g (0.033 mol NaH) of a 53% sodium hydride mineral oil dispersion,[9] and 125 ml of absolute dimethylformamide. The solution was stirred and gassed with a stream of dry air for 52 hr at room temperature. The solution first turned red and then yellow. After removal of the solvent *in vacuo* the residue was treated with water and then extracted with chloroform. The chloroform layer was dried and concentrated to give 2.4 g of oil. Chromatography on silica gel ($CHCl_3$ eluent) gave 1.82 g (77%) of 2-aminobenzophenone (7a): mp 100–101° (lit.[10] mp 102°); ir (KBr), 2.92 and 3.02 (OH), 6.11 (C=O), 6.72, 6.85, and 7.98 μ; uv, λ_{max}^{EtOH} 236 mμ (ϵ 21,460) and 379 mμ (ϵ 5880).

B. 3-Phenyl-5-Chloroxindole (6b).—The procedure used to oxidize 6a was followed.

From 5.0 g (0.02 mol) of 3-phenyl-5-chloroxindole, 1.8 g (0.04 mol NaH) of 53% sodium hydride mineral oil dispersion, and 250 ml of absolute dimethylformamide there was obtained 6.0 g of oil (contains mineral oil). Chromatography on silica gel ($CHCl_3$ eluant) gave 3.6 g (79%) of 2-amino-5-chlorobenzophenone (7b): mp 96–98° (C_6H_6–pentane) (lit.[11] mp 98–100°) uv, λ_{max}^{EtOH} 238 mμ (ϵ 25,670) and 391 mμ (ϵ 12,835).

C. 3-Phenyl-5-Methoxyindole (6c).—The procedure used to oxidize 6a was followed.

From 1.5 g (0.006 mol) of 3-phenyl-5-methoxyoxindole, 0.9 g (0.02 mol NaH) of 53% sodium hydride mineral oil dispersion, and 100 ml of absolute dimethylformamide there was obtained 1.6 g of an oil (contains mineral oil). Chromatography on silica gel ($CHCl_3$–C_6H_6, 1:1 eluent) gave 1.4 g of oil that crystallized from ether to give 0.93 g (68%) of 2-amino-5-methoxybenzophenone (7c): mp 51° (lit.[12] 51–52°); ir (KBr), 2.92 and 3.01 (NH_2) and 6.12 μ (C=O).

Air Oxidation of the Sodium Salt of 1-Methyl-3-Phenyloxindole (6d).—To a flask equipped with a magnetic stirring bar, gas inlet tube, and a calcium chloride drying tube there was added 5.0 g (0.023 mol) of 1-methyl-3-phenyloxindole, 1.2 g (0.026 mol NaH) of a 53% sodium hydride dispersion, and 300 ml of absolute dimethylformamide. The solution was stirred and gassed at ambient temperature with a stream of dry air for 8 hr. The clear yellow solution was then concentrated *in vacuo*. The residue was neutralized with 2 *N* HCl and then extracted with ethyl acetate. The acetate solution was washed with saturated sodium chloride, water, and then dried with magnesium sulfate. Removal of the solvent gave 5.3 g of oil. Crystallization from a pentanemethylene chloride–carbon tetrachloride mixture gave 1.9 g of 1-methyl-3-phenyldioxindole (8), mp 137–138°. The mother liquor was concentrated to give 4.2 g of oil that contained two components with R_f 0.28 and 0.80 ($CHCl_3$–CH_3OH, 95:5). Chromatography of this mixture through a silica gel column (C_6H_6 eluent) gave 0.3 g of an oil A (R_f 0.28) and 2.3 g of 8, (R_f 0.80), mp 138–141°.

Recrystallization of the 4.2 g of crude 8 from methanol gave 3.9 g (71%) of 8: mp 139–141°; ir (KBr), 2.98 (OH) and 5.81 μ (C=O); ir (CH_2Cl_2), 2.83 and 2.96 (LH) and 5.81 μ (C=O); nmr ($CDCl_3$), 3.09 (3 H, singlet, CH_3) and 4.28 ppm (1 H, singlet, OH); uv, λ_{max}^{EtOH} 210 mμ (ϵ 30,150), 258 (6300), and 290 (1230).

Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.3; H, 5.5; N, 5.9; O, 13.4. Found: C, 74.8; H, 5.5; N, 5.8; O, 13.4.

Crystallization of the oil A from pentane gave 0.27 g (7%) of 2-methylaminobenzophenone[13] (7d): mp 65° (lit.[13] 66° and 69°); ir (CCl_4), 3.02 (NH), and 6.16 μ (C=O); uv, λ_{max}^{EtOH} 236 mμ (ϵ 20,750) and 396 mμ (ϵ 6730); nmr ($CDCl_3$), 2.12 (1 H, singlet, NH), 2.88 (3 H, singlet, CH_3), 6.58 (2 H, quartet, aromatic H) and 7.20–7.82 ppm (7 H, multiplet, aromatic H).

Air Oxidation of the Sodium Salt of 3-Phenyl-2-Cumaranone (9).—The 3-phenyl-2-cumaranone (9) was prepared by the procedure of Elderfield and King[14] from phenol and DL-mandelic acid. It had mp 112–113° (lit.[14] mp 110–111°); ir (KBr), 5.57 μ (lactone C=O); nmr ($CDCl_3$), 4.82 (1 H, singlet, –CH) and 7.06–7.50 ppm (9 H, multiplet, C_6H_5 and C_6H_4).

To a flask equipped with a magnetic stirring bar, gas inlet tube, and a calcuim chloride drying tube there was added 4.0 g (0.019 mol) of 9, 200 ml of dry dimethylformamide, and 2.6 g (0.014 mol NaH) of sodium hydride as a 53% dispersion in mineral oil. The pale yellow solution was stirred and dry air was bubbled through the solution at room temperature for about 56 hr. The solution first turned green and then changed back to yellow after several hours. The dimethylformamide was removed *in vacuo*. The residue was treated with 25 ml of HCl and then extracted with chloroform. The chloroform was washed with saturated sodium chloride solution and water. After drying with magnesium sulfate the chloroform was removed to give 6.7 g of oil (contains mineral oil). The oil was taken up in methanol and treated with water until crystals formed. The substance was separated to give 3.60 g of solid, mp 158–167°. Tlc on silica gel ($CHCl_3$–CH_3OH 95:5) revealed two components, (R_f 0.20 and R_f 0.85). Vacuum sublimation (1.5 mm) at 100° (bath temperature) gave 0.150 g of oil (R_f 0.85, trace 0.20), and at 170° there was obtained an additional 2.70 g of solid, mp 166–169° (R_f 0.20). Chromatography of the oil on silica gel (developed with $CHCl_3$ and eluted with $CHCl_3$–CH_3OH, 95:5) gave 0.110 g (5%) of 2-hydroxybenzophenone (10): mp 41° (lit.[15] 39–40°); R_f 0.85; ir (CCl_4), 3.10 (OH) and 6.16 μ (C=O); uv, λ_{max}^{EtOH} 259 mμ (ϵ 11,720) and 338 mμ (ϵ 4220). Comparison of the infrared and ultraviolet spectrum of 10 with those of an authentic sample[16] of 2-hydroxybenzophenone showed them to be identical.

The crystalline fraction recrystallized from CCl_4–$CHCl_3$ to give 2.40 g (52%) of 4-phenyl-1,3-benzodioxan-4-ol-2-one (11): mp 170–172°; R_f 0.20 ($CHCl_3$–CH_3OH 95:5); ir (KBr), 3.20–4.05 (broad, ionic OH), 5.80 (O–CO–O), 6.72, 7.01, 7.36, 7.82, 8.12, and 8.93 μ; uv, λ_{max} 218 mμ (ϵ 6090) and 282 mμ (ϵ 4040) in ethanol and λ_{max} 283 mμ (ϵ 4840) in 5% KOH–ethanol; nmr ($CDCl_3$), 6.88 (4 H, singlet), 7.21–7.84 (5 H, multiplet), and 9.02 ppm (1 H, exchangeable, OH). The mass spectrum exhibits a molecular ion peak at *m/e* 242 ($C_{14}H_{10}O_4$) with abundant fragment peaks at *m/e* 197 ($M^+ - HCO_2$), 105 ($C_6H_5CO^+$), and 77 ($C_6H_6^+$). The pK_{mcs}* value[17] was 5.5.

(9) Metal Hydrides Co., Beverly, Mass.

(10) K. Suzuki, E. K. Weisburger, and J. B. Weisburger, *J. Org. Chem.*, **26**, 2239 (1961).

(11) G. N. Walker, *ibid.*, **27**, 1929 (1962).

(12) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *ibid.*, **27**, 3781 (1962).

(13) H. Staudinger and N. Kon, *Ann. Chem.*, **384**, 38 (1911); F. Ullmann and H. Bleier, *Chem. Ber.*, **35**, 4273 (1902).

(14) R. C. Elderfield and T. P. King, *J. Amer. Chem. Soc.*, **76**, 5439 (1954).

(15) E. Moriconi, W. F. O'Connor, and W. F. Forbes, *ibid.*, **82**, 5454 (1960).

(16) K & K Laboratories, Plainview, N. Y.

(17) The value of pK_{mcs}*, the apparent pK_a value in a mixture of 80% methyl Cellosolve and 20% water was determined by the procedure of Simon: W. Simon, *Helv. Chim. Acta*, **41**, 1835 (1958).

Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.5; H, 4.2; O, 26.3. Found: C, 69.7; H, 4.3; O, 26.0.

Lithium Aluminum Hydride Reduction of 4-Phenyl-1,3-Benzodioxan-4-ol-2-one (11).—A solution of 1.3 g (0.0054 mol) of **11** in 25 ml of dry tetrahydrofuran was added dropwise in about 0.5 hr to a stirred slurry of 2.0 g (0.05 mol) of lithium aluminum hydride in 50 ml of tetrahydrofuran. The mixture was blanketed with nitrogen and refluxed for 120 hr. After cooling in an ice bath the reactants were treated with 4.0 ml of 2 *N* sodium hydroxide, 6.0 ml of water, and 25 g of anhydrous sodium sulfate. The salts were filtered off and washed with tetrahydrofuran. The combined filtrates were concentrated to give 0.9 g (73%) of 4-phenyl-1,3-benzodioxan-4-ol (**12**): mp 73–75° (diethyl ether–pentane); ir (KBr), 2.29 (OH), 3.43, 6.72, 7.92, 8.05, 9.36, and 10.30 μ; uv, λ_{max} 230 mμ (ϵ 2955), 279 (shoulder, 3200), 283 (4220), and 289 (shoulder, 3210) in ethanol and λ_{max} 279 mμ (shoulder, ϵ 7050), 283 (7240), and 289 (shoulder, 5440) in 5% KOH–ethanol; nmr ($CDCl_3$), 2.43 (1 H, exchangeable, OH), 3.92 (2 H, broad singlet, O–CH_2O), 6.78 (4 H, singlet), and 7.20–7.78 ppm (5 H, multiplet). The mass spectrum exhibits a molecular ion peak at *m/e* 228 ($C_{14}H_{12}O_3$) with abundant fragment peaks at *m/e* 197 ($M^+ - CH_3O$), 105 ($C_6H_5CO^+$) and 77 ($C_6H_5^+$). The pK_{mcs}* value[17] was 9.5.

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.7; H, 5.3; O, 21.0. Found: C, 73.6; H, 5.4; O, 21.2.

Registry No.—N-*p*-Chlorophenyl-DL-mandelamide, 10295-53-1; N-*p*-methoxyphenyl-DL-mandelamide, 15815-96-0; **6b**, 15815-97-1; **6c**, 15757-31-0; **8**, 15757-32-1; **11**, 15757-33-2; **12**, 15757-34-3.

Acknowledgment.—The authors express their appreciation to Mr. Urs Stoeckli and his associates for determining analytical and instrumental data.

The Synthesis and Desulfurization of 2,3,3-Trichloro- and 2,2,3-Trichlorothioxanes[1]

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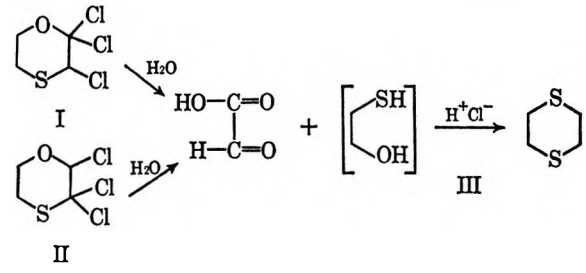
In the course of a research project on fluorinated derivatives of ethers and thioethers, it became of interest to synthesize some chlorinated derivatives of 1,4-thioxane as intermediates. We chose 1,4-thioxane because it contains both ether and thioether linkages in the ring.

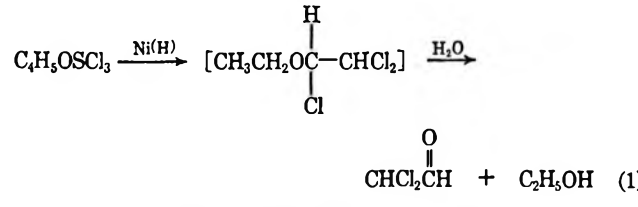
Only a few references to the chlorinated derivatives of 1,4-thioxane are noted in the literature. Haubein[3,4] reported the preparation of several chlorothioxanes, among them a trichlorothioxane, but did not determine the positions of the chlorine atoms on the ring in the case of the trichlorothioxane. By a modification of the Haubein procedure[4] we have recently synthesized and identified two trichlorinated derivatives of 1,4-thioxane, $C_4H_5OSCl_3$. When 1,4-thioxane is chlorinated in a CCl_4 solution at 80° and 75 g/hr, a white crystalline compound, $C_4H_5OSiCl_3$, melting at 58° is isolated in 90% yield. If the rate is increased to 150 g/hr, a white crystalline compound melting at 53° is isolated in 93% yield. These compounds are stable when kept free of moisture but fume in moist air with the elimination of HCl and have a characteristic obnoxious odor. They impart slight irritation when in contact with the skin.

Aqueous hydrolysis of both compounds yields glyoxylic acid and β-mercaptoethanol which was isolated as dithiane under these conditions.[5] The hydrolysis products show that all three chlorine atoms were substituted on the same side of the thioxane ring.



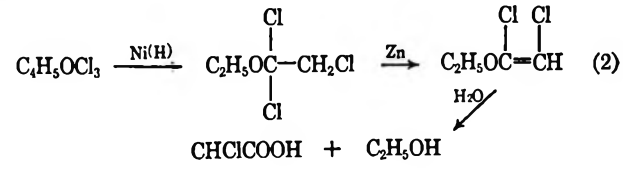
Since the instability of these compounds made structure determination difficult, desulfurization was decided upon as an unambiguous method.

It was found that an active preparation of Raney nickel, Raney nickel "C,"[6] could be used to desulfurize the trichlorinated compounds without causing hydrogenolysis of the chlorine atoms. The compound melting at 53° was desulfurized according to the reaction in eq 1.

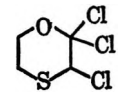


The α,α,β-trichloroethyl ether was not isolated but was hydrolyzed in solution. Identification of the hydrolysis products dichloroacetaldehyde and ethanol was taken as proof that the compound melting at 53° was 2,3,3-trichlorothioxane.

Desulfurization of the compound melting at 58° took place according to eq 2. In this case the heretofore



unknown α,α,β-trichloroethyl ether was hydrolyzed to monochloroacetic acid in solution. The desulfurization products confirmed that the compound melting at 58° is 2,2,3-trichlorothioxane.



The chlorination of 1,4-thioxane at 145° to give 2,3,3-trichlorothioxane is consistent with the chlorination

(1) We are indebted to the U. S. Air Force command for partial support of this work under Contract No. 49(633)-283 monitored by ARDC.

(2) All inquiries should be addressed to this author at General Electric Silicone Products Department, Waterford, N. Y.

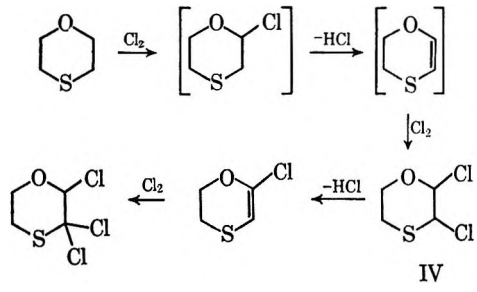
(3) A. H. Haubein, U. S. Patent 2,766,169 (1956).

(4) A. H. Haubein, *J. Amer. Chem. Soc.*, **81**, 144 (1959).

(5) E. Swistak, *Comp. Rend.*, **240**, 1544 (1955).

(6) C. D. Hurd and B. Rudner, *J. Amer. Chem. Soc.*, **73**, 5157 (1951).

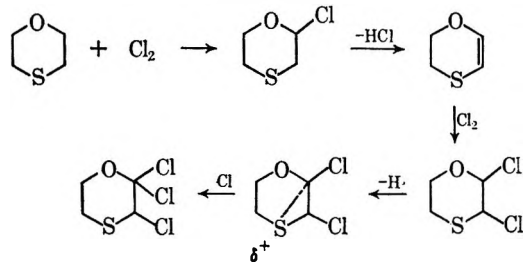
SCHEME I



IV

and thermal dehydrohalogenation of ethyl ether[7] (Scheme I). However, an entirely different mechanism must be postulated for the chlorination at 80° to give 2,2,3-trichlorothioxane. The dichloride IV is known to be stable at 80°[8] and it is highly unlikely that the chlorine atoms α to the sulfur atom would be removed in preference to the more active one in the β position (α to the ether linkage). Instead, it is more probable that the last step in this reaction is a free-radical process with no olefin being formed. Theoretically, the homolytic cleavage of the hydrogen α to oxygen could be anchimerically assisted and the resulting radical stabilized by a sulfur bridge (Scheme II). This theory is supported by the work of Kwart

SCHEME II



and Evans,[9] which suggests that sulfur is able to perform this function with greater facility than oxygen and thus causes the radical formed in the position β to sulfur to be more stable.

Experimental Section

Chemicals.—The 1,4-thioxane used in this study was donated by the New Product Division of the Thiokol Chemical Corp. This compound was freed of peroxides by known procedures and distilled. The fraction boiling at 147–150° was used. The Raney nickel used in this study was obtained from the E. H. Sargent Co. as a 50% nickel, 50% aluminum alloy. It was converted into Raney nickel "C" by the method of Hurd.[7] The solvent methyl Cellosolve (ethylene glycol monomethyl ether) was obtained from Fisher Chemical Co. and purified by distillation. Chlorine gas was obtained from the Matheson Co. in cylinders.

General.—All melting points were uncorrected and determined on a Fisher-Johns melting point apparatus. Elemental analyses were by Galbraith Laboratories in Knoxville, Tenn. All reactions were carried out in light.

2,3,3-Trichlorothioxane.—To a 1-l. flask fitted with a mechanical stirrer, Friedrich's reflux condenser, thermometer, and coarse fritted-glass dispersing device were added 208 g (2.0 mol) of 1,4-thioxane and 350 ml of carbon tetrachloride. The mixture was stirred and heated to reflux. The heating was discontinued and chlorine gas was introduced at approximately 150 g/hr. When approximately 6 mol of chlorine had been added, the reaction mixture was kept at −5° until complete precipitation occurred. This required 20–24 hr. The white crystalline material was filtered and washed with cold ligroin. One recrystallization from a 1:5 ethyl ether–ligroin mixture and decolorizing charcoal gave 290 g (93% yield) of pure trichlorothioxane, mp 53°. *Anal.* Calcd for $C_4H_5OSCl_3$: Cl, 51.25; S, 15.45. Found: Cl, 51.29; S, 15.46.

2,2,3-Trichlorothioxane.—In a procedure similar to the one above, 104 g (1.0 mol) of 1,4-thioxane in 300 ml of carbon tetrachloride was chlorinated as 80° with 225 g of chlorine at a rate of 75 g/hr. The reaction mixture worked up in the above manner gave 185 g (90%) of white crystals melting at 58°. *Anal.* Calcd for $C_4H_5OSCl_3$: Cl, 51.25; S, 15.45. Found: S, 51.60; Cl, 15.30.

Hydrolysis of Trichlorothioxane Melting at 53°.—A 10-g sample of the trichlorothioxane in 50 ml of water was heated to boiling, stoppered, and shaken for 1 hr. Glyoxylic acid was isolated from the solution as the 2,4-dinitrophenylhydrazone, mp 191–192° (lit.[10] mp 190° dec), and did not depress the melting point of an authentic sample of glyoxylic acid, 2,4-dinitrophenylhydrazone. The 1,4-dithiane (mp 110–111°) was sublimed from the solution and did not depress the melting point of dithiane prepared by an unambiquous route.

The hydrolysis of trichlorothioxane melting at 58° was accomplished by the above procedure with the same products being isolated.

Desulfurization of 2,3,3-Trichlorothioxane in Methyl Cellosolve.—To a stirred solution of 35 g (0.336 mol) of trichlorothioxane (mp 53°) in 500 ml of dry methyl Cellosolve was added 150 g of Raney nickel "C." An ice bath was applied to keep the spontaneous reaction mixture at 10°. After the exothermic period was over, the reaction mixture was gradually heated to 60° and kept at this temperature for 12 hr. The Raney nickel was decanted and centrifuged in a clinical centrifuge to separate the remainder of the nickel. It was observed that the obnoxious odor of the trichlorothioxane had disappeared and the product had a pleasant odor.

The resulting α,β,β-trichloroethyl ether was hydrolyzed to give dichloroacetaldehyde and ethanol. The dichloroacetaldehyde was isolated as the 2,4-dinitrophenylhydrazone mp 146–150° (lit.[11] mp 146°). Further hydrolysis converted the dichloroacetaldehyde into glyoxal which was isolated as the 2,4-dinitrophenylosazone, mp 317° (lit.[12] mp 318° dec), and the bissemicarbazone, mp 270° (lit.[13] mp 270°).

Desulfurization of 2,2,3-Trichlorothioxane in Diethylcarbitol.—Diethylcarbitol (250 ml) was made anhydrous by predrying with sodium sulfate and distilling from sodium ribbon. To this was added 100 g of Raney nickel "C" and 10 g of 2,2,3-trichlorothioxane (mp 58°). The reaction mixture was stirred with a mechanical stirrer and let react for 7 days at room temperature. The reaction mixture was separated from the Raney nickel as above. The desulfurized mixture (50 g) was added to 2 g of mossy zinc and refluxed for 1 hr. The zinc chloride was filtered off and the filtrated distilled through a Vigreux column. The fraction boiling at 120–130° was collected. This fraction fumed in moist air, gave positive tests for unsaturation, and was assumed to be $CH_3CH_2OCCl{=}CHCl$. Hydrolysis of the above distillate by refluxing 10 g of it in 10 g of H_2O for 1 hr gave monochloroacetic acid. This was identified as the *p*-phenylphenacyl ester, mp 115° (lit.[14] 116°), and did not depress the melting point of an authentic sample of the *p*-phenylphenacyl ester of monochloroacetic acid.

Acknowledgment.—We gratefully acknowledge the help of Fred Jones, Clyde Bishop, and Curtis Harper who prepared the trichlorothioxanes while graduate students at the Carver Research Foundation.

(7) G. E. Hull and F. M. Ubertini, *J. Org. Chem.*, **15**, 715 (1956).
(8) A. H. Haubein, U. S. Patent 2,725,331 (1955).
(9) H. Kwart and E. R. Evans, *J. Org. Chem.*, **31**, 413 (1966).
(10) "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1965, p 1543.
(11) A. Ross and R. N. Ring, *J. Org. Chem.*, **26**, 581 (1961).
(12) See ref 10, p 1542.
(13) "Chemical Rubber Handbook of Tables for Organic Compounds," 3rd ed, Chemical Rubber Co. Press, Cleveland, Ohio.
(14) N. Drake and J. Bronitsky, *J. Amer. Chem. Soc.*, **52**, 3719 (1930).

Formation of Derivatives of Cyclopentane-1,3-dione from Oxazolones

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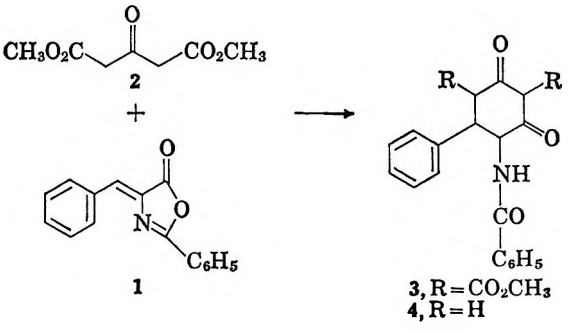
It has recently been shown[1] that the oxazolone **1** reacts with dimethyl 3-oxoglutarate (**2**) to give the dihydroresorcinol **3** in 90% yield. This reaction has

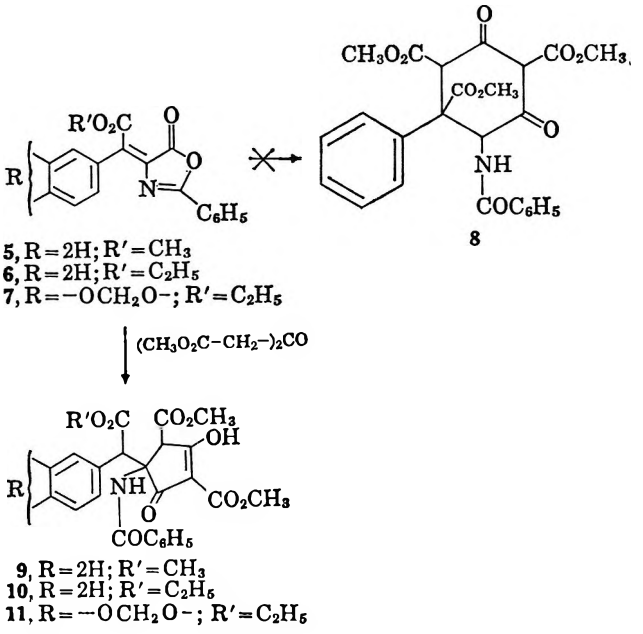


2 + **1** → **3**, R = CO_2CH_3; **4**, R = H

been successfully applied in the synthesis of the polyfunctional 6-deoxy-6-demethyltetracycline.[2]

In the course of an attempted application of this reaction to the now completed total synthesis of the Amaryllidaceae alkaloid crinine,[3] the oxazolone **5** was prepared. When this compound was allowed to react with dimethyl 3-oxoglutarate (**2**) and sodium hydride in tetrahydrofuran, conditions which previously had been used in the preparation of **3**, a single crystalline product was isolated in 44% yield. This compound had the elemental composition ($C_{25}H_{23}NO_9$) of a 1:1 adduct of oxazolone **5** to dimethyl 3-oxoglutarate as required for a dihydroresorcinol derivative of structure **8**. In addition, like **3**, it gave a brownish ferric chloride test. However, a comparison of the ultraviolet spectra between **3** and the condensation product seemed to exclude such a possibility. The dihydroresorcinol **3** had an absorption maximum at 250 mμ in methanol which was not altered on addition of acid but was shifted to 277 mμ on addition of base. In contrast, the condensation product from **5** had an absorption maximum at 254 mμ in methanol which was shifted to 225 mμ on addition of acid but remained at 254 mμ when base was added. This showed that the new reaction product had to be a considerably stronger acid than the dihydroresorcinol **3**. The compound seemed to be almost completely dissociated in neutral methanol, since upon addition of base only very minor spectral changes were observed. Upon addition of acid, the absorption maximum of the undissociated species at 225 mμ was observed. Therefore, it was evident that the new compound could not be a derivative of a dihydroresorcinol. This information, plus that derived from the nmr spectrum, led to the assignment of structure **9**, with a cyclopentane-1,3-dione chromophore, to the condensation product from the oxazolone **5**.

The nmr spectrum of the new compound, recorded in deuteriochloroform, revealed four sharp singlets at δ 3.49, 3.66, 3.69, and 3.90 which integrated for nine protons and were assigned to the three methyl ester groups.[4] The multiple peaks assigned to the ester protons may be interpreted in terms of an acid–base equilibrium and a tautomeric equilibrium of the acid which was set up in solution. Eleven protons absorbed as a multiplet at δ 7.1–9.8 (ten aromatic protons and one amide proton). The integration in this area dropped to ten protons upon addition of D_2O due to facile exchange of the amide proton. A broad singlet at δ 11.68 (enolic OH) also disappeared on addition of D_2O. This singlet always integrated for less than one proton (dissociation). Finally, two singlets integrating for one proton each were observed at δ 4.68 and 3.82. The signal at δ 4.68 was assigned to the benzylic hydrogen in **9**, and the remaining signal at δ 3.82 was assigned to the lone ring hydrogen in the



5, R = 2H; R′ = CH_3
6, R = 2H; R′ = C_2H_5
7, R = $-OCH_2O-$; R′ = C_2H_5

$(CH_3O_2C-CH_2-)_2CO$

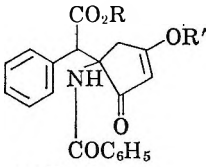
9, R = 2H; R′ = CH_3
10, R = 2H; R′ = C_2H_5
11, R = $-OCH_2O-$; R′ = C_2H_5

cyclopentanedione ring. This proton was exchanged more rapidly than the proton at δ 4.68 when **9** was treated with alkaline D_2O.

The structure of **9** was further substantiated by chemical transformations. Compound **9** was saponified with barium hydroxide and then decarboxylated with warm hydrochloric acid to give the acid **12** in 74% yield. The ultraviolet spectrum of **12** is similar to that of cyclopentane-1,3-dione and distinctly different from the corresponding degradation product **4**[1] of the cyclohexane-1,3-dione derivative **3**. On treatment with 1 equiv of diazomethane, **12** was transformed into its methyl ester **13**, but both **12** and **13**, when treated with excess diazomethane, were converted into the enol ether methyl ester **15** or its isomer. Further, the conversion of the acid **12** into the enol ether **14** proceeded under the conditions described by Wenkert.[5]

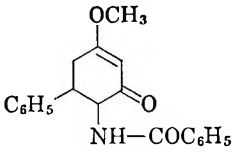
(1) H. Muxfeldt, J. Bebling, G. Grethe, and W. Rogalski, *J. Amer. Chem. Soc.*, **89**, 4991 (1967).
(2) H. Muxfeldt and W. Rogalski, *ibid.*, **87**, 933 (1965).
(3) H. Muxfeldt, R. S. Schneider, and J. B. Mooberry, *ibid.*, **88**, 3670 (1966).
(4) In other solvent systems (methanol-d_4 and D_2O–sodium carbonate) the esters were never observed as three singlets but rather as four or five lines.
(5) E. Wenkert and D. P. Strike, *ibid.*, **86**, 2044 (1964).

On treatment of **14** with diazomethane, **15** was formed in high yield. The ultraviolet spectrum of enol ethers **14** and **15** no longer exhibit the bathochromic shift



12, R = R′ = H
13, R = CH_3; R′ = H
14, R = H; R′ = CH_3
15, R = R′ = CH_3

characteristic of β-diketones upon addition of base. Furthermore, their absorption maximum was different from that of the cyclohexane derivative **16**.



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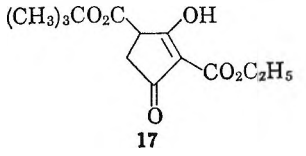
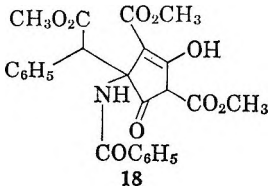
All the reported data are in good agreement with structure **9** for the condensation product. The strong acidity of **9** and its effect on the pH dependency of the ultraviolet spectrum was very similar to the behavior of compound **17**.[6] The only significant



17

difference being that **17** had an absorption maximum at 248 mμ (ε 21,000) in acidic solution, whereas the absorption maximum of compound **9** appeared at 225 mμ (ε 23,000) with a shoulder at approximately 250 mμ. This may be explained best by the assumption that tautomer **18** contributed substantially to the tautomeric mixture of **9** since **18** appeared to have minimal nonbonded interactions. Therefore, it might appear to a much larger extent in the equilibrium of **9** than the corresponding tautomer **19** does in the equi-



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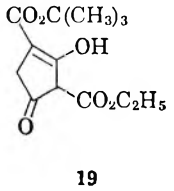
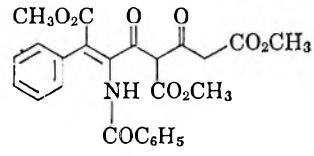


19

librium of **17**. The oxazolones **6** and **7** condensed in the same way that oxazolone **5** condensed with dimethyl 3-oxoglutarate (**2**), and the cyclopentane-1,3-dione derivatives **10** and **11** were obtained in 55 and 35% yields, respectively.

One way of rationalizing the formation of a cyclopentane-1,3-dione instead of a cyclohexane-1,3-dione is to assume that the oxazolone (for example, **5**) is first opened by the anion of dimethyl 3-oxoglutarate (**2**) to form the β-keto ester **20**. Then **20** could undergo



20

an intramolecular Michael addition to give **9**. On the basis of the available experimental data other reasonable pathways cannot, of course, be excluded.

(6) G. Büchi and E. C. Roberts, *J. Org. Chem.*, **33**, 460 (1968). We thank these authors for communicating their data to us prior to its publication.

Experimental Section[7]

Preparation of Oxazolone 5.—To a solution of 765 mg (4.61 mmol) of methyl benzoyl formate, bp 85–88° (3.5 mm), and 825 mg (4.61 mmol) of hippuric acid in 1.4 ml of acetic anhydride and 10 ml of tetrahydrofuran (distilled from lithium aluminum hydride) was added 870 mg (2.3 mmol) of lead acetate trihydrate, and the reaction was boiled under reflux for 6 hr and then stirred at room temperature for 10 hr. The solution was diluted with methylene chloride and washed with water. After drying of the organic phase over sodium sulfate and evaporation of the solvent *in vacuo*, 1.58 g of a red oil was obtained, which upon addition of ethanol and ether gave 577 mg (33% of theory) of **5**: mp 124–125°; λ_{max}^{KBr} 5.60, 5.70, 5.75, and 6.15 μ; $\lambda_{max}^{95\%\ ethanol}$, mμ (ε), 365 (33,050), sh 385 (21,000), sh 350 (29,000), and 261 (14,650).

Anal. Calcd for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.23; N, 4.55; mol wt, 307. Found: C, 70.61; H, 4.45; N, 4.88.

The preparation of oxazolone 6 was similar to that described for the preparation of the oxazolone **5**; the ethyl ester oxazolone **6** was prepared from 4.44 g (24.7 mmol) of ethyl benzoyl formate and 1 equiv each of hippuric acid and lead acetate trihydrate. The mixture was boiled under reflux for 19 hr. After crystallization from ether 2.3 g (29% of theory) of **6** was isolated. A sample was recrystallized for analysis from ether: mp 122–123°; λ_{max}^{KBr} 5.55, 5.65, 5.75, and 6.05 μ; $\lambda_{max}^{95\%\ ethanol}$, mμ (ε), 365 (32,800), sh 385 (21,580), sh 350 (28,400), 261 (13,220), and sh 248 (11,900).

Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.35; mol wt, 321. Found: C, 71.00; H, 4.71; N, 4.34.

Preparation of Oxazolone 7.—A mixture of 1.1 g (4.74 mmol) of ethyl piperonyl formate, 844 mg of hippuric acid, 1.80 g (4.74 mmol) of lead acetate trihydrate, and 1.45 g of acetic anhydride was dissolved in 10 ml of tetrahydrofuran and boiled under reflux in a manner similar to that described for the preparation of the methyl ester oxazolone **5**. After work-up, 1.9 g of a thick red oil was obtained, which could be partially crystallized upon addition of ether. A yield of 580 mg (33% of theory) of yellow crystalline **7** was isolated. An analytical sample was recrystallized from ether: mp 160–161°; λ_{max}^{KBr} 5.55, 5.65, 5.75, and 6.13 μ; λ_{max}^{ether}, mμ (ε), 410 (27,700), 396 (29,150), 334 (10,050), 295 (9,560), 268 (18,300), and 258 (15,220).

Anal. Calcd for $C_{20}H_{15}NO_6$: C, 65.75; H, 4.14; N, 3.83; mol wt, 365. Found: C, 65.83; H, 4.09; N, 3.79.

Condensation of Oxazolone 5 with Dimethyl 3-Oxoglutarate.—To a solution of 309 mg (1.0 mmol) of **5** and 209 mg (1.2 mmol) of dimethyl 3-oxoglutarate dissolved in 10 ml of tetrahydrofuran was added 26.4 mg (1.1 mmol) of sodium hydride, and the solution was stirred under a nitrogen atmosphere for 18 hr at room temperature. The clear yellow solution was diluted with water and the resulting alkaline solution was washed with chloroform. The aqueous solution was then acidified and extracted with chloroform. This extract was dried over sodium sulfate and evaporated. A 364-mg portion of alkali soluble yellow oil was obtained, and upon addition of methanol–ether, 217 mg (44% of theory) of white crystalline solid **9** was precipitated. The remaining oil exhibited a maximum at 232 and a shoulder at 260 mμ in alkaline methanol. A sample of **9** was recrystallized from methanol–ether, mp 146–150°. A dilute solution of **9** in methanol gave an immediate orange coloration upon addition of ferric chloride: λ_{max}^{KBr} 2.95, 5.7–5.8 (broad), 6.0, and 6.22 μ; $\lambda_{max}^{0.4\ N\ HCl\text{-}MeOH}$, mμ (ε), sh 250 (19,250) and 225 (23,000); $\lambda_{max}^{0.1\ N\ HCl\text{-}MeOH}$, mμ (ε), 251 (21,250) and 226 (22,000); λ_{max}^{MeOH}, mμ (ε), 255 (25,550) and sh 227 (19,600); $\lambda_{max}^{0.1\ N\ NaOH\text{-}MeOH}$, mμ (ε), 253 (26,600) and sh 225 (20,900); $\lambda_{max}^{acetonitrile}$, mμ (ε), 250 (19,500), and 222 (23,950).

(7) Melting points were taken on a Kofler hot stage.

Anal. Calcd for $C_{25}H_{23}NO_9$: C, 62.36; H, 4.95; N, 2.91; mol wt, 481. Found: C, 62.40; H, 5.08; N, 2.82.

Condensation of Oxazolone 6 with Dimethyl 3-Oxoglutarate.—In a manner identical with that described for the reaction of oxazolone 5, 878 mg (2.74 mmol) of 6 was allowed to react with 570 mg (3.28 mmol) of dimethyl 3-oxoglutarate and 75.5 mg (3.15 mmol) of sodium hydride. A yield of 1.27 g of a yellow oil was obtained which, upon addition of methanol–ether, gave 746 mg (55% of theory) of 10: mp 140–144°. An analytical sample was obtained from methanol–ether: λ_{max}^{KBr} 2.9, 5.7, 5.75, 5.95, and 6.2 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 254 (23,000), and 227 (19,800); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ), 254 (24,900) and sh 227 (19,450); nmr ($CDCl_3$), δ 1.15 (t, J = 7 cps, 3 H, -O-CH_2-**CH_3**), 4.1 (q, J = 7 cps, 2 H, O-**CH_2**-CH_3), 3.52 (s, 3 H, methyl ester), 3.93 (3 H methyl ester), 3.76 (s, 1 H, methine), 4.70 (s, 1 H, benzylic methine), and 7.2–7.9 (m, 11 H, aromatic and N-H).

Anal. Calcd for $C_{26}H_{25}NO_9$: C, 63.02; H, 5.08; N, 2.82; mol wt, 495.5. Found: C, 63.13; H, 5.02; N, 2.74.

Condensation of Oxazolone 7 with Dimethyl 3-Oxoglutarate.—A 622-mg (1.7 mmol) sample of 7, 355 mg (2.04 mmol) of dimethyl 3-oxoglutarate, and 46.5 mg (1.95 mmol) of sodium hydride were dissolved in 10 ml of tetrahydrofuran. After 3.5 days at room temperature the mixture was worked up in the usual fashion and gave 584 mg of a yellow oil. A yield of 308 mg (34% of theory) of a white solid (11) was obtained after crystallization from methanol–ether: mp 150–158°; λ_{max}^{KBr} 2.9, 5.7, 5.8, 6.0, 6.25, and 9.7 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 250 (24,570) and sh 290 (4700); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ), 251 (26,180) and sh 290 (5850); nmr ($CDCl_3$), δ 1.11 (t, J = 7 cps, 3 H, O-CH_2-**CH_3**), 4.1 (q, J = 7 cps, 2 H, O-**CH_2**-CH_3), 3.57 (s, 3 H, methyl ester), 3.95 (s, 3 H, methyl ester), 3.77 (s, 1 H, methine), 4.67 (s, 1 H, benzylic methine), 5.99 (s, 2 H, methylenedioxy), and 6.7–8.0 (m, 10 H, aromatic and N-H).

Anal. Calcd for $C_{27}H_{25}NO_{11}$: C, 60.11; H, 4.67; N, 2.59; mol wt, 539.5. Found: C, 60.03; H, 4.81; N, 2.54.

Hydrolysis and Decarboxylation of 9.—To a solution of 500 mg (1.04 mmol) of 9 in 10 ml of hot methanol, 100 ml of a 5% barium hydroxide solution in water was added. The mixture was heated on a steam bath for 2 hr. During this time a white precipitate formed from the initially colorless, homogeneous solution. The mixture was then acidified with 1 *N* HCl and heated for an additional 10 min. During this time the acid 12 crystallized. After cooling, 270 mg (74%) of 12 was collected, mp 261°. An analytical sample was recrystallized from methanol–ether: λ_{max}^{KBr} 3.0, 2.7–4.4 (broad), 5.9, 6.15, and 6.22 μ; λ_{max}^{MeOH}, mμ (ϵ), 249 (17,550) and 225 (17,550); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ) 268 (21,500) and 225 (15,780).

Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.98; mol wt, 351.4. Found: C, 68.37; H, 4.93; N, 3.93.

Preparation of the Ester Enol Ether 15 from 12.—To a cold solution of 130 mg (0.356 mmol) of 12 in 10 ml of ether was added a solution of diazomethane (0.80 mmol). Another portion of diazomethane was added after 4 hr and the mixture stirred at room temperature for 18 hr. The solvent was removed *in vacuo* and a sample of the recovered foam exhibited no bathochromic shift in alkaline methanol. A sample was crystallized from ether, mp 142–144°. Recrystallization of 15 from methanol–ether gave a 1:1 methanol adduct: mp 83–85°; λ_{max}^{KBr} 3.0, 5.8, 5.92, 6.05, and 6.3 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 243 (20,850) and sh 225 (18,900); $\lambda_{max}^{0.01\ N\ methanol\text{-}NaOH}$, m$\mu$ (ϵ), 243 (20,850) and sh 225 (18,900); nmr ($CDCl_3$), δ 3.22 (AB, J = 17 cps, 2 H, methylene), 3.75 (s, 6 H, enol ether and methyl ester), 4.02 (s, 1 H, benzylic methine), 5.23 (s, 1 H, vinyl), and 7.2–8.0 (m, 11 H, aromatic and N-H).

Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.95; H, 5.58; N, 3.69; mol wt, 379.4. Found: C, 69.89; H, 5.48; N, 3.72.

Preparation of the Acid Enol Ether 14.—A 378-mg (1.08 mmol) portion of 12 and 10 mg of *p*-toluenesulfonic acid was dissolved in 75 ml of benzene and 50 ml of methanol and distilled over 5 hr to a volume of 30 ml. The solution was diluted with ether and washed with dilute alkali. The organic phase was dried over sodium sulfate and evaporated to dryness under reduced pressure to give 41 mg (8% of theory) of the ester enol ether 15, mp 140–144°. The alkaline solution was then acidified and washed with chloroform. The combined organic extracts were washed with water, dried over sodium sulfate, and evaporated to give 446 mg (62% of theory) of 14: mp 125–128°; λ_{max}^{KBr} 2.95, 2.7–4.4 (broad), 5.85, 6.0, 6.3, and 7.35 μ; $\lambda_{max}^{methanol}$, mμ (ϵ), 243 (19,050) and sh 228 (18,050); $\lambda_{max}^{alkaline\ methanol}$, m$\mu$ (ϵ), 228 (19,650) and sh 240 (18,900); nmr (D_2O-NaOD), δ 3.0 (d AB pattern, 2 H, methylene), 3.30 (s, 3 H, enol ether), 3.58 (s, 1 H, methine), 4.8 (s, HOD), 5.18 (s, 1 H, vinyl), and 7.0–8.0 (m, 10 H, aromatic).

Anal. Calcd for $C_{21}H_{19}NO_5 \cdot CH_3OH$: C, 66.48; H, 5.83; N, 3.54; mol wt, 402. Found: C, 66.71; H, 5.54; N, 3.61.

Preparation of the Ester Enol Ether 15 from 14.—To a suspension of 590 mg (1.61 mmol) of the acid enol ether 14 in 10 ml of cold ether was added a solution of diazomethane (4.8 mmol). Immediately upon addition of the diazomethane the solution became homogeneous. After 30 min a white solid crystallized from the cold solution. Stirring was continued for 12 hr and the excess diazomethane was removed by warming the solution slightly under reduced pressure. A 550-mg (86%) portion of the ester enol ether 15 was collected and shown to be identical with that prepared directly from 12.

Registry No.—**5,** 15924-08-0; **6,** 15924-09-1; **7,** 15963-73-2; **9,** 15924-10-4; **10,** 15924-11-5; **11,** 15924-12-6; **12,** 15924-13-7; **14,** 15924-14-8; **15,** 15924-15-9.

Acknowledgment.—This work was supported by a National Institute of Health Predoctoral Fellowship given to Richard S. Schneider and by the National Science Foundation (Grant No. GP-6626).

Preparation of Tertiary N,N-Dimethylamines by the Leuckart Reaction

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Introduction of alkyl groups into ammonia or a primary or secondary amine by means of certain aldehydes or ketones, when the reducing agent is ammonium formate, is known as the Leuckart reaction.[2,3] Later, Wallach[4] obtained better yields by using a mixture of ammonia or substituted amine with formic acid. The Leuckart reaction did not come into general use as a preparative method until 1936 when Ingersoll and coworkers[5] reviewed the subject and applied the reaction to the synthesis of a series of substituted β-phenylethylamines. Similarly, Novelli[6] showed that respectable yields of secondary amines could be obtained by the action of N-alkylformamides on some substituted acetophenones. When the carbonyl compound is formaldehyde, the transformation is termed the Clarke–Eschweiler[3] method.

The Leuckart reaction applied to the synthesis of tertiary amines has found only limited application to date. Early examples of the reaction where an aldehyde or ketone has been treated with a dialkylformamide include the reaction of benzaldehyde with formylpiperidine to give N-benzylpiperidine,[4] and the conversion

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(2) R. Leuckart, *Ber.*, **18**, 2341 (1885); R. Leuckart and E. Bach, *ibid.*, **19**, 2128 (1886).

(3) M. L. Moore, *Org. Reactions*, **5**, 301 (1949).

(4) O. Wallach, *Ann.*, **343**, 54 (1905).

(5) A. W. Ingersoll, J. H. Brown, C. K. Kim, W. D. Beauchamp, and G. Jennings, *J. Amer. Chem. Soc.*, **58**, 1808 (1936).

(6) A. Novelli, *ibid.*, **61**, 520 (1939).

TABLE I

TERTIARY AMINES SYNTHESIZED[a]

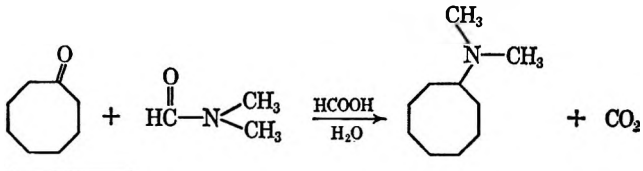
Ketone	Tertiary amine product	% yield of amine	% yield of methiodide	Picrate mp, °C
Cyclopentanone	N,N-Dimethylcyclopentylamine	61		176.5–178[b]
Cyclohexanone	N,N-Dimethylcyclohexylamine	70	61[m]	178.5–179.5[c]
Cycloheptanone	N,N-Dimethylcycloheptylamine	55	71	186–187[d]
Cyclooctanone	N,N-Dimethylcyclooctylamine[f]	75		197–198[e]
Cyclodecanone	N,N-Dimethylcyclodecylamine	76		145–146[g]
2-Octanone	N,N-1-Trimethylheptylamine	65		59.5–61.5[h]
Acetophenone	N,N,α-Trimethylbenzylamine	58		138–139[i]
3-Pentanone	N,N-Dimethyl-1-ethylpropylamine	38		180.5–181.5[j]
Norcamphor	*endo*-2-Dimethylaminonorbornane[k]	70		220–222[l]

[a] See Experimental Section for procedure. [b] Lit.[10] 177–178°. [c] Lit.[10] 175–176°. [d] M. Mousseron, R. Jacquier, and H. Christol [*Compt. Rend.*, **235**, 57 (1952)] reported mp 184°. [e] C. G. Overberger, M. A. Klotz, and H. Mark [*J. Amer. Chem. Soc.*, **75**, 3186 (1953)] reported mp 195.8–197.4°. [f] Submitted for publication in *Org. Syn.* [g] A. C. Cope, R. J. Cotter, and G. G. Roller [*J. Amer. Chem. Soc.*, **77**, 3590 (1955)] reported mp 145.8–147.4°. [h] *Anal.* Calcd for $C_{16}H_{26}N_4O_7$: C, 49.73; H, 6.78; N, 14.50. Found: C, 49.57; H, 6.95; N, 14.83. This compound was recrystallized twice from ethanol. All other melting points are reported after one recrystallization from ethanol. [i] G. Wittig, R. Mangold, and G. Felletschin [*Ann.*, **560**, 116 (1948)] reported mp 137–138°. [j] A. C. Cope, N. A. LeBel, H. H. Lee, and W. R. Moore [*J. Amer. Chem. Soc.*, **79**, 4720 (1957)] reported mp 180.5–182.5°. [k] The product is believed to be almost entirely the *endo* isomer. The *endo*-amine has a strong band in the infrared at 795 cm^{-1} which is absent in the spectrum of the *exo* isomer. Furthermore, the *exo* isomer has a strong band at 1022 cm^{-1} and a medium band at 820 cm^{-1}, both of which are absent in the spectrum of the *endo* isomer (see ref 17). [l] Reported 218–220° for the *endo* isomer; see ref 17. [m] The crude N,N-dimethylcyclohexylamine was converted into its methiodide without purification (see Experimental Section) and had mp 280–281° dec. A. Skita and H. Rolfes [*Ber.*, **53**, 1242 (1920)] reported mp 277°.

of furfural into N,N-dimethylfurfurylamine.[3,7,8] Subsequently, Bunnett and Marks[9] prepared six tertiary amines from ketones and dialkylformamides and obtained yields ranging from 21 to 54%. However, they found that the reactions failed to give tertiary amines in the absence of magnesium chloride catalysis.

An all encompassing mechanism for the Leuckart reaction has not been reported. Mousseron[10] has studied the action of formamide and N-mono- and N,N-dialkylformamides on cyclopentanones and cyclohexanones in an effort to establish the mechanism of this reaction. As a result of a deuterium-labeling study, Rekashera and Miklukhin[11] have argued against the mechanism proposed by Mousseron. In contradiction to the common opinion on the ionic mechanism[3,10,11] postulated for the Leuckart reaction, Lukasiewicz[12] has suggested that this reaction and the reduction of imines by formic acid take place according to a free-radical mechanism.

Our initial efforts in this area were directed toward the synthesis of N,N-dimethylcyclooctylamine which heretofore had been prepared by a number of less direct routes.[10,13–15] When cyclooctanone was treated with dimethylformamide and formic acid in an autoclave at 190°, the desired amine was obtained in good yield (75%). The crude product, isolated after acid and then base extraction, was pure to vpc and could be used without distillation in subsequent reactions (see the Experimental Section for details). The only by-product isolated from the reaction was cyclooctanol (10%), in addition to recovered cyclooctanone (10%). Optimum yields were obtained in the temperature range of 175–190°. Lowering the temperature to 160° reduced the yield of tertiary amine, although at the lower temperature very little reduction to cyclooctanol occurred. Reaction times of 8–16 hr were employed.



The demand for tertiary N,N-dimethylamines as synthetic intermediates in the Hofmann elimination and the Cope elimination[16] prompted us to examine the general synthetic utility of this reaction for preparing tertiary amines. Our experiments are summarized in Table I. The reaction gave a good yield with a relatively hindered bicyclic ketone and appears to be quite general for cyclic ketones. Its use in the preparation of *endo*-2-dimethylaminonorborane is worthy of note since this compound has previously been prepared only by a multistep route.[17,18] Likewise the reaction afforded reasonable yields of tertiary amines with methyl ketones. However, as the acyclic ketones become more highly substituted, the yields decreased. For example 3-pentanone afforded a 38% yield of N,N-dimethyl-1-ethylpropylamine, and considerably lower yields were obtained with diisopropyl ketone, 4-heptanone, benzophenone, and α-tetralone. However, no effort was made to increase the yields in these cases by altering the reaction conditions or by the use of Lewis acid catalysis.[9,10] This reaction appears to be the method of choice for the conversion of cyclic and relatively unhindered acyclic ketones into tertiary amines because of the ease of manipulation and the good yields of easily purified products.

(7) F. P. Nabenbauer, Abstracts, 93rd National Meeting of the American Chemical Society, Chapel Hill, N. C., April 1937; U. S. Patent 2,185,220 (1940).

(8) E. A. Weilmuenster and C. N. Jordan, *J. Amer. Chem. Soc.*, **67**, 415 (1945).

(9) J. F. Bunnett and J. L. Marks, *ibid.*, **71**, 1587 (1949).

(10) (a) M. Mousseron, R. Jacquier, and R. Zagdoun, *Bull. Soc. Chim. Fr.*, 197 (1952); (b) *ibid.*, 596 (1957).

(11) A. F. Rekashera and G. P. Miklukhin, *J. Gen. Chem. USSR*, **26**, 2407 (1956).

(12) A. Lukasiewicz, *Tetrahedron*, **19**, 1789 (1963).

(13) A. C. Cope and W. J. Bailey, *J. Amer. Chem. Soc.*, **70**, 2305 (1948).

(14) V. K. Ziegler and H. Wilms, *Ann.*, **567**, 1 (1950).

(15) A. C. Cope and L. L. Estes, Jr., *J. Amer. Chem. Soc.*, **72**, 1128 (1950).

(16) A. C. Cope and E. R. Trumbull, *Org. Reactions*, **11**, 317 (1960).

(17) A. C. Cope, E. Ciganek, and N. A. LeBel, *J. Amer. Chem. Soc.*, **81**, 2799 (1959).

(18) W. E. Parham, W. T. Hunter, R. Hanson, and T. Labr, *ibid.*, **74**, 5646 (1952).

Experimental Section

An Example of a Procedure for the Synthesis of Tertiary Amines in Table I. N,N-Dimethylcyclooctylamine.—To a glass-lined[19] high pressure autoclave, arranged for agitation by rocking, was placed 100 g (0.79 mol) of cyclooctanone, 100 g of 90.5% formic acid, and 175 g of dimethylformamide. The autoclave was heated at 190°, under autogenous pressure, for 16 hr. The autoclave was allowed to cool and was vented in a hood.

The pale yellow homogeneous solution was slowly added to a separatory funnel containing 500 ml of a 10% hydrochloric acid solution and the aqueous amine hydrochloride was washed several times with ether.[20] The aqueous phase was treated with a solution of 70 g of sodium hydroxide in 200 ml of water (basic to litmus paper) and the N,N-dimethylcyclooctylamine was recovered by extracting with two 500-ml portions of ethyl ether. The ethereal layer was dried ($MgSO_4$) and the ether was removed under reduced pressure to afford 98 g of crude amine as a light-colored oil.

The amine was distilled under reduced pressure through a short Vigreux column. The product was collected at 63° (3 mm), $n^{25}D$ 1.4710 [lit.[15] bp 79–80 (6 mm), $n^{25}D$ 1.4706].

Cycloheptyltrimethylammonium Iodide.—In a glass-lined high pressure autoclave was placed 56.1 g (0.5 mol) of cycloheptanone, 64 g of 90.5% formic acid, and 110 g of dimethylformamide. The autoclave was heated at 190° for 14 hr and then was cooled to room temperature.

The pale yellow solution was slowly added to a separatory funnel containing 300 ml of 10% hydrochloric acid solution. The aqueous amine hydrochloride was extracted twice with 250-ml portions of ethyl ether. The aqueous layer was cooled and sodium hydroxide was added until the solution was decidedly basic. The N,N-dimethylcycloheptylamine was recovered by extracting with two 250-ml portions of ethyl ether. The ethereal layer was dried ($MgSO_4$) and the solvent was removed, at reduced pressure.

The crude amine was converted into its methiodide without further purification. Methyl iodide (100 g) was added dropwise to a stirred solution of the crude amine in 150 ml of methanol maintained at 0°. The ice bath was removed and the reaction mixture was stirred 3 hr at room temperature. The yellow solution was then poured into 1 l. of ethyl ether, filtered, and washed with ethyl ether to give 101 g (71.3%) of cycloheptyltrimethylammonium iodide that had mp 263.5–264° dec (lit.[21] mp 259°).

Registry No.—I, 15924-18-2; II, 15924-19-3.

(19) When the reaction was carried out in a stainless steel high-pressure autoclave without the use of a glass liner, the yield of product was greatly reduced and a considerable amount of cyclooctanol was obtained as the major product.

(20) The combined ether layers were dried ($MgSO_4$) and the ether was removed under pressure to afford 21 g of an approximately 1:1 mixture of cyclooctanone and cyclooctanol.

(21) R. Willstatter, *Ann.*, **317**, 204 (1901).

Oxidations of Amines. V. Duality of Mechanism in the Reactions of Aliphatic Amines with Permanganate[1]

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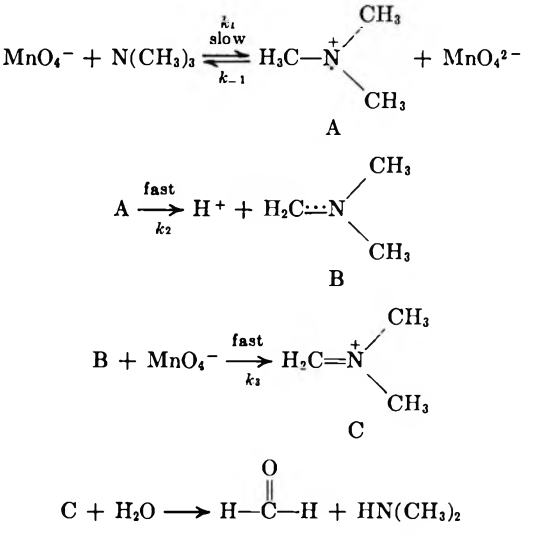
The mechanism of permanganate oxidation of aliphatic amines, *i.e.*, electron *vs.* hydrogen atom or hydride abstraction in the rate-determining step k_1, as well as the relative reactivities of aliphatic primary, secondary, and tertiary amines with permanganate ion in nearly neutral aqueous solutions are unresolved questions of current interest.[2,3] Whereas one would infer from an early investigation by Vorländer, Blau, and Wallis[4] that the order of reactivity should be tertiary > secondary > primary, Lambert and Jones have quoted the opposite conclusions[2a] from the literature.[2b] This confusion may be the result of a reversal in order of reactivity on change from neutral to acidic permanganate. Stewart[5] has stated that oxidation of trimethylamine by permanganate involves an initial attack on the C–H bond adjacent to the nitrogen.

Recognizing the similarity between permanganate and chlorine dioxide[6] oxidation of aliphatic amines, we tentatively propose, for discussion purposes, the mechanism in Scheme I for permanganate oxidation of trimethylamine. The manganate formed in Scheme I reacts to give manganese dioxide as in eq 1. This

SCHEME I



$$3MnO_4^{2-} + 2H_2O \longrightarrow 2MnO_4^- + MnO_2 + 4OH^- \quad (1)$$

reaction is too fast to enter into the kinetics under the pH conditions chosen for this study.[3] The product, formaldehyde, has been detected. This product is analogous to the benzaldehyde obtained by Wei and Stewart[3] from permanganate oxidation of benzylamine; as was shown by these investigators, the reactive amine species is the free base.

Our experience with chlorine dioxide in amine oxidations[6] led us to believe that both α-hydrogen atom transfer and electron transfer mechanisms can occur simultaneously, depending on the structure of the amine, on the oxidizing species, etc. Indeed, benzylamine, studied by Wei and Stewart,[3] is one of the most likely amines to react by α-hydrogen transfer, both because it is a primary amine (see below) and because

(1) Paper number IV of this series: W. H. Dennis, Jr., L. A. Hull, and D. H. Rosenblatt, *J. Org. Chem.*, **32**, 3783 (1967).

(2) (a) D. G. Lambert and M. M. Jones, *J. Amer. Chem. Soc.*, **88**, 4615 (1966). (b) H. Schechter, S. S. Rawalay, and M. Tubis, *ibid.*, **86**, 1701 (1964); H. Schechter and S. S. Rawalay, *ibid.*, **86**, 1706 (1964).

(3) M. Wei and R. Stewart, *ibid.*, **88**, 1974 (1966).

(4) D. Vorländer, G. Blau, and T. Wallis, *Ann.*, **345**, 261 (1906).

(5) R. Stewart in "Oxidation in Organic Chemistry," part A, K. B. Wiberg, Ed., Academic Press Inc., New York, N. Y., 1965, p 61.

(6) (a) D. H. Rosenblatt, A. J. Hayes, Jr., B. L. Harrison, R. A. Streaty, and K. A. Moore, *J. Org. Chem.*, **28**, 2790 (1963); (b) D. H. Rosenblatt, L. A. Hull, D. C. DeLuca, G. T. Davis, R. C. Weglein, and H. K. R. Williams, *J. Amer. Chem. Soc.*, **89**, 1158 (1967); (c) L. A. Hull, G. T. Davis, D. H. Rosenblatt, H. K. R. Williams, and R. C. Weglein, *ibid.*, **89**, 1163 (1967).

the free radical formed in the hydrogen transfer process is resonance stabilized by the benzene ring.

We determined kinetic rate constants for the oxidation of trimethylamine and perdeuteriotrimethylamine with permanganate. An isotope effect of 1.84 on the ratio of the true second-order rate constants, k_H/k_D, was observed (Table I). The value of the isotope effect for

TABLE I
EXPERIMENTAL DATA

Amine[d]	k,[a] l. mol^{-1} sec^{-1}	pK_a
$(C_2H_5)_3N$	3.08×10^1	10.65[b]
$(C_2H_5)_2NH$	9.44×10^{-1}	10.98[b]
$(C_2H_5)NH_2$	8.28×10^{-2}	10.63[b]
$(CH_3)_3N$	3.36	9.92[c]
$(CD_3)_3N$	1.82	10.155[c]

[a] $k = k_{obsd}([H^+] + K_a)/K_a$(the anal. concn. of amine), $k_1 = 1.5k$. [b] H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78**, 2570 (1956). [c] See ref 6. The pK_a of trimethylamine was determined at 0.49 ionic strength and was found to have the same value that was found at 0.2 ionic strength. [d] Registry no. for these amines follow in descending order: 121-44-8, 109-89-7, 75-04-7, 75-50-3, 13960-80-0.

trimethylamine thus lies in the upper part of the range usually associated with secondary isotope effects (below 2.0).[7] At least two possible explanations may be involved for the somewhat high value. (1) The additive secondary isotope effect of nine α hydrogens, already great by sheer weight of numbers, is enhanced by the nature of the reaction, in that a planar aminium cation radical is formed.[8] (2) Both hydrogen abstraction and electron abstraction are simultaneously operative, with electron abstraction playing a predominant role. Whereas the observation of an isotope effect of 1.84 would not normally rule out rate-determining C–H bond cleavage, we believe that the other evidence supports this view. This evidence is the previous observation by Wei and Stewart[3] of an isotope effect of 7.0 for oxidation of benzylamine by permanganate (thus demonstrating that primary isotope effects of amine oxidation with permanganate tend to be large) and the observation of large secondary isotope effects (1.3 to 1.8)[6] in the formation of aminium cation radicals. (In the latter instance, the mechanism of electron abstraction was corroborated by independent means.) These rationalizations have one element in common, namely that the reaction of permanganate with trimethylamine must involve electron abstraction and cannot be considered exclusively or even predominantly hydrogen transfer.

It should be noted, furthermore, that, in the reaction of ferricyanide[2] and nitrous acid[9] with tertiary amines, electron transfer has been proposed for the former, and hydrogen elimination from an N-nitrosoammonium intermediate has been proposed for the latter in the rate-determining step, but kinetic evidence for the proposed mechanisms (*i.e.*, kinetic isotope studies) is lacking. It is thus even more significant that, in the present case and in the only other case[6c] so far subjected to the kinetic isotope effect test, electron abstraction has been found to play an important mechanistic role, the extent of electron abstraction *vs.* hydrogen abstraction depending on the nature of the amine.

Kinetic rate constants for oxidation of the series triethylamine, diethylamine, and ethylamine by permanganate were determined and it was found that the order of reactivity for this series is tertiary > secondary > primary (Table I). This order of reactivity is not as Lambert and Jones[1] inferred, but conforms to that observed for chlorine dioxide[6] and ferricyanide.[10]

We believe that this order of reactivity will show most pronounced differences when the mechanism is that of pure electron abstraction. However, the same order of reactivity can prevail for the *dual mechanism* of electron abstraction and hydrogen abstraction. As we have previously shown,[6c] benzyl-*t*-butylamine reacts faster with chlorine dioxide than does benzylamine, and the former goes mainly by the electron-abstraction path. The general tendency appears to be that electron abstraction will dominate the reactivities of tertiary amines, but hydrogen abstraction is of increased importance as one goes to secondary and then primary amines. This may be due to the fact that a substituent on the nitrogen atom will affect the electron density of the nitrogen atom to a significantly greater degree than it will affect the bond strength of the α-carbon–hydrogen bond. Therefore, the relative reactivities will mostly reflect the changes in electron density at the nitrogen atom rather than the more remote electronic influences on the α-carbon–hydrogen bond. The value of the rate constant for electron abstraction will thus increase to a greater degree than the value of the hydrogen abstraction rate constant with an increase in aliphatic substitution on the nitrogen. It is entirely reasonable for an oxidation that proceeds principally by hydrogen abstraction for a primary amine to shift to one that is much faster and goes almost exclusively by electron abstraction as the change is made to secondary and then to tertiary amine.

Experimental Section

Kinetics.—The kinetics were followed with a Cary Model 14 spectrophotometer at 525 mμ. An excess of amine (usually about 0.01 M) was permitted to react with 8×10^{-5} M potassium permanganate at 25 ± 1° (0.166 M phosphate buffers, pH 7.5–pH 8.0, and 0.49 ionic strength). These experiments were within the very narrow range of conditions under which the Mn(IV) invariably produced in such oxidations does not come out as a manganese dioxide precipitate[11] until after the permanganate oxidation is complete. Thus it was possible to follow the strictly first-order disappearance of MnO_4^- spectrophotometrically. This was done by plotting $(A - A_\infty)$ against time. The trimethylamine-d_9 hydrochloride was obtained from Volk Radiochemical Co., labeled 99% D.

Isolation of Formaldehyde as the Dimedone Derivative.—In 125 ml of water was placed 0.010 mol of potassium permanganate and 0.015 mol of trimethylamine hydrochloride, and the pH was adjusted to 8. After 5 min, the solution was filtered and 4.21 g of dimedone in 1000 ml of hot water was added at pH 11. After 30 min, the pH was adjusted to 4.0 and the dimedone derivative of formaldehyde, mp 189–190°, was isolated in 19% yield (0.84 g).

(7) K. B. Wiberg, "Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964, p 354.

(8) S. I. Miller, *J. Phys. Chem.*, **66**, 978 (1962); A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, **80**, 2326 (1958).

(9) P. A. S. Smith and R. N. Loeppky, *ibid.*, **89**, 1147 (1967).

(10) T. D. Perrine, *J. Org. Chem.*, **16**, 1303 (1951).

(11) The failure of MnO_2 to precipitate for reasonably long periods of time under these reaction conditions is probably due to stabilization of dissolved Mn(IV) by phosphate ions, as noted by R. Stewart ("Oxidation Mechanisms: Applications to Organic Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1964, p 60).

A Novel Class of Disulfides. The SS-2-Acetaminoethyl-O,O-dialkyl Thioperoxymonophosphorothionates[1]

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There is continuing interest in the chemistry of cysteamine, 2-aminoethanethiol, particularly in cysteamine derivatives in which the mercapto group has been transformed into a disulfide-type linkage.

$NH_2CH_2CH_2SX$

1a, X = $SCH_2CH_2NH_2$[2]
b, X = SO_3Na[3]
c, X = $\overset{\overset{O}{\|}}{S}CH_2CH_2NH_2$[4]
d, X = SR[3,4]

Cysteamine and its derivatives are also among the most potent materials offering protection against ionizing radiation.[5]

It is believed that the SS-2-acetaminoethyl-O,O-dialkyl thioperoxymonophosphorothionates, where one-

$(RO)_2\overset{\overset{S}{\|}}{P}SSCH_2CH_2NH\overset{\overset{O}{\|}}{C}CH_3$

2

half of the unsymmetrical disulfide is 2-acetaminoethyl and the other is the good leaving group, O,O-dialkylphosphorothioyl, would offer more protection against ionizing radiation than cystamine **1a** and would be less toxic than 2-aminoethanethiol.

The method of Field, *et al.*,[4] using mercaptans and 2-acetaminoethyl 2-acetaminoethanethiolsulfonate (**3**) was used to prepare **2** (eq 1). The crude product was

$$\underset{\mathbf{3}}{AcNHCH_2CH_2\overset{\overset{O}{\|}}{S}\overset{\overset{O}{\|}}{S}CH_2CH_2NHAc} + \underset{\mathbf{4}}{(RO)_2\overset{\overset{S}{\|}}{P}SH} \longrightarrow \underset{\mathbf{2}}{AcNHCH_2CH_2S\overset{\overset{S}{\|}}{S}P(OR)_2} + \underset{\mathbf{5}}{AcNHCH_2CH_2SO_2H} \quad (1)$$

R = C_3H_7, *i*-C_3H_7, or C_4H_9

purified by column chromatography using 200 mesh Florisil and the method of Patchett and Batchelder.[6]

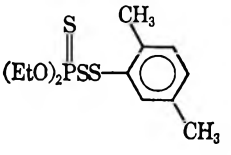
For yield data, see Table I. The products had absorption bands in the infrared spectrum for NH (3300 cm^{-1}), —C(=O)NH— (1655 cm^{-1}, 1550 cm^{-1}), and phosphate (980 cm^{-1}). All preparations also yielded some tetraalkyl thioperoxydiphosphorothionate (**6**) which arises from the disproportionation of **2**. The infrared spectra of **6** had bands for phosphate at 980 cm^{-1} but no bands for —NH— or —C(=O)NH—. The **6** where R = *i*-C_3H_7 is solid and was further identified by its melting point.

When 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride was used in place of the acetamino compound, only the two symmetrical disulfides, cystamine dihydrochloride (**7**) and **6**, were obtained.

$\underset{\mathbf{6}}{(RO)_2\overset{\overset{S}{\|}}{P}S\overset{\overset{S}{\|}}{S}P(OR)_2}$ $\underset{\mathbf{7}}{NH_2CH_2CH_2SSCH_2CH_2NH_2\cdot 2HCl}$

No reaction was obtained when the Bunte salt of cysteamine (**1b**) was allowed to react with **4**, even when heated at reflux with methanol as the solvent.[7]

Almasi and Paskucz[8] reported the preparation of SS-2,5-dimethylphenyl-O,O-diethyl thioperoxymonophosphorothionate (**8**) from diethoxyphosphinothioylsulfenyl chloride (**9**) and 2,5-dimethylbenzenethiol, and Michalski, *et al.*,[9] reported the preparation of SS-butyl-O,O-diethyl thioperoxymonophosphorate (**10**) from butanethiol and diethoxyphosphinylsulfenyl chloride (**11**). Similar reactions of dialkoxyphosphinyl-



8

$\underset{\mathbf{10}}{(EtO)_2\overset{\overset{O}{\|}}{P}SSC_4H_9}$

$\underset{\mathbf{9}}{(EtO)_2\overset{\overset{S}{\|}}{P}Cl}$ $\underset{\mathbf{11}}{(EtO)_2\overset{\overset{O}{\|}}{P}Cl}$

sulfenyl chlorides or dialkoxyphosphinothioylsulfenyl chlorides with cysteamine, cysteamine hydrochloride, or sodium 2-aminoethylmercaptide gave only the symmetrical disulfides. The unsymmetrical disulfides formed but disproportionated under the conditions of the reaction. Such disproportionations are well known in the chemistry of disulfides.[10]

Experimental Section[11]

SS-2-Acetaminoethyl-O,O-dialkylmercapto Phosphorodithioates (2).—A mixture of 13.5 g (0.05 mol) of 2-acetaminoethyl 2-acetaminoethanethiolsulfonate,[4] 0.05 mol of O,O-dialkylphosphorodithioic acid, and 100 ml of acetone was allowed to stand at room temperature for 5 days. Some 2-acetaminoethanesulfinic acid had crystallized from the reaction mixture as a white solid. The solvent was removed on a rotary evaporator at reduced

(1) This investigation was supported by Contract No. DA-49-193-MD-2914 from U. S. Army Medical Research and Development Command, Walter Reed Army Institute of Research.

(2) E. J. Mills, Jr., and M. T. Bogert, *J. Amer. Chem. Soc.*, **62**, 1173 (1940).

(3) D. L. Klayman, J. D. White, and T. R. Sweeney, *J. Org. Chem.*, **29**, 3737 (1964).

(4) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Amer. Chem. Soc.*, **83**, 4414 (1961).

(5) A. Pihl and L. Eldjarn, *Pharmacol. Rev.*, **10**, 437 (1958).

(6) G. G. Patchett and G. H. Batchelder, *J. Agr. Food Chem.*, **9**, 395 (1961).

(7) W. Lorenz, German Patent 1,112,068 (Feb 12, 1960).

(8) L. Almasi and L. Paskucz, *Chem. Rev.*, **98**, 613 (1965).

(9) J. Michalski, B. Borecka, T. Kapecka, and H. Strzelecka, *Rocz. Chem.*, **33**, 1255 (1959).

(10) A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 583 (1959).

(11) All melting points were uncorrected and were taken with a Mel-Temp apparatus.

TABLE I

$(RO)_2P(S)SCH_2CH_2NHAc$

R	Yield, %	$n^{25}D$	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	P, % Calcd	P, % Found	S, % Calcd	S, % Found
C_3H_7	22	1.5420	36.24	36.11	6.69	6.77	4.23	4.16	9.34	9.13	29.02	28.83
i-C_3H_7	27	1.5375[a]	36.24	35.95	6.69	6.67	4.23	4.47	9.34	9.16	29.02	29.06
C_4H_9	39	1.5345	40.09	39.84	7.28	7.39	3.89	3.73	8.61	8.09	26.55	26.55

[a] Solidified upon standing, recrystallized from benzene–petroleum ether (mp 40–42°).

pressure to give a pasty solid. This crude product was mixed with 25 ml of cyclohexane–benzene 1:1 mixture, filtered, and washed with more solvent to separate out the remaining sulfinic acid. The solvent was removed from the combined filtrates to give an amber oil. This oil was chromatographed on an 18 in. × 1 in. column filled with 125 g of 200 mesh Florisil. The sample was put on and then developed with 400 ml of cyclohexane–benzene 1:1, 200 ml of benzene, and then 400 ml of chloroform. The cyclohexane–benzene fraction contained the alkylthioperoxyphosphorothionates.[12]

The benzene and chloroform fractions were rechromatographed as before. The benzene and chloroform fractions were combined, and the solvents were removed under high vacuum on a rotary evaporator to give the SS-2-acetaminoethyl-O,O-dialkyl thioperoxymonophosphorothionates.

Registry No.—2 (R = propyl), 15790-97-3; 2 (R = isopropyl), 15790-98-4; 2 (R = butyl), 15790-99-5.

(12) In cases where R = i-C_3H_7, the thioperoxy compound was a solid, mp 90–91° [lit. 90–91°, N. I. Zimbyanksii, O. A. Prib, and B. S. Dreck, *Zh. Obshch. Khim.*, **31**, 880 (1961)]. *Anal.* Calcd for $C_{17}H_{28}O_4P_2S_4$: C, 33.79; H, 6.62. Found: C, 33.79; H, 6.58.

Kinetics of Hydrolysis of the Tetramethyl Ketal of *p*-Benzoquinone[1]

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One of the more interesting features of the kinetics of hydrolysis of ortho esters is the lack of parallelism between substrate reactivity and stability of the corresponding carbonium ions which are evidently formed as the products of the rate-determining step.[3] Thus, ethyl orthocarbonate is less reactive than ethyl orthobenzoate which is less reactive than ethyl orthoformate.[4] In fact, ortho esters are generally less reactive than ketals. Thus, reactivities are inversely related to the expected carbonium ion stabilities within this series. This behavior has been suggested to result from considerations regarding substrate basicity,[4,5] substrate stabilization through double-bond–no-bond resonance,[6] and saturation effects.[7] In contrast, the rates of hydrolysis of acetals and ketals appear to be correlated well, for the most part, with stabilities of the derived carbonium ions.[8,9] However, Kreevoy and Taft have observed that the rates of hydrolysis of diethyl ketals derived from benzophenone and fluorenone are substantially less than would have been predicted on the basis of expected resonance stabilization of the corresponding carbonium ions.[10,11] This behavior was rationalized on the basis that as the transition state became increasingly stable relative to starting material it would be reached progressively earlier and, hence, would possess less carbonium ion character and be less susceptible to stabilization by resonance.[12] A related argument has been applied to the kinetics of hydrolysis of ortho esters.[13] While such arguments certainly will have validity in some cases, there seems to be a reasonable limitation to their applicability. *Thus, a change in substrate structure which would impart additional stabilization to the transition state relative to the ground state will not alter the transition state structure to such an extent that the structural change actually results in a less reactive substrate.*

We now wish to report an additional apparent lack of correlation between carbonium-ion stability and substrate reactivity for ketal hydrolysis.

Acid-catalyzed hydrolysis of the tetramethyl ketal of *p*-benzoquinone(3,3,6,6-tetramethoxy-1,4-cyclohexadiene) proceeds in two distinct steps, the first reaction being about 300 times more rapid than the second. The intermediate exhibits a shoulder in the ultraviolet spectrum near 235 mμ and is almost certainly the monoketal (6,6-dimethoxy-1,4-cyclohexadien-3-one). The product is *p*-benzoquinone as evidenced by its absorption spectrum and by direct isolation.[14] First-order rate constants for both the hydrolysis and decomposition of the intermediate in aqueous solution at 25° and ionic strength 0.50 are collected as a function of pH in Table I. Both reactions are seen to be first order in hydrogen ion activity: formation of the monoketal has a second-order rate constant of 650 M^{-1} sec^{-1} and the hydrolysis of this species a corresponding value of 2.1 M^{-1} sec^{-1}. The greater reactivity of the diketal is certainly expected since the electron-withdrawing properties of the carbonyl function present in the monoketal should destabilize the carbonium ion formed from the latter species with respect to that derived from the former. What is surprising is that the diketal is about an order of magnitude less reactive than 2,2-dimethoxy-

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(2) Career Development Awardee of the National Institutes of Health.

(3) For a discussion of this and related points, see E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1967).

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(12) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(13) R. H. DeWolfe and J. L. Jensen, *ibid.*, **85**, 3264 (1963).

(14) B. Belleau and N. L. Weinberg, *ibid.*, **85**, 2525 (1963).

TABLE I
FIRST-ORDER RATE CONSTANTS FOR HYDROLYSIS OF THE TETRAMETHYL KETAL OF *p*-BENZOQUINONE IN AQUEOUS SOLUTION AT 25° AS A FUNCTION OF pH[a]

Formation of intermediate		Decomposition of intermediate	
pH	$10^3 k_{obsd.}$, sec^{-1}	pH	$10^3 k_{obsd.}$, sec^{-1}
5.60	1.83	3.36	0.987
5.56	1.925	3.36	0.917
5.45	2.52	3.02	2.18
5.12	5.13	2.80	3.47
4.94	7.53	2.79	3.27
4.90	6.30	2.61	4.13
4.77	10.66	2.43	6.86
4.56	15.06	2.42	9.47

[a] Dilute acetate, and chloroacetate buffers employed in appropriate ranges of pH. The formation of the intermediate was followed at 280 mμ, its decomposition at 245 mμ.

propane.[8,15] The cross-conjugated carbonium ion derived from the diketal of *p*-benzoquinone should certainly be a great deal more stable than that derived from 2,2-dimethoxypropane and, hence, one might well have expected the former species to be very much the more reactive. The explanation for the opposite result is not clear. This observation does suggest that those factors which account for the related behavior observed with ortho esters may be important for the determination of reactivities of at least some ketals as well.

Experimental Section

We are indebted to Dr. Bernard Belleau for providing a sample of *p*-benzoquinone tetramethyl ketal.[14] The sample provided was recrystallized twice from petroleum ether (bp 60–80) prior to use in kinetic measurements, mp 44°. Kinetic measurements were performed spectrophotometrically with the aid of a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder through which water from a thermostated bath was continuously circulated. Formation of the reaction intermediate was followed at 280 and its decomposition at 245 mμ. All reactions were carried out at 25°, ionic strength 0.50, in aqueous solution containing 3% acetonitrile. First-order rate constants were calculated in the usual fashion and second-order rate constants by dividing the first-order constants by the activity of hydrogen ions. Values of pH were obtained with the aid of a Radiometer PHM 4c pH meter. Distilled water was employed throughout.

Registry No.—Tetramethyl ketal of *p*-benzylquinone 1579-103-4.

(15) The data for comparison, obtained by Kreevoy and Taft[8] refer to 50% dioxane solutions. Previous work in this laboratory (K. Koehler, unpublished observations) indicates that rates for reactions of the type of interest here are slowed by about an order of magnitude in 50% aqueous dioxane compared with water. This factor has been employed in arriving at the indicated rate ratio.

The Photocycloaddition of Diphenylacetylene to 2,3-Dihydropyran

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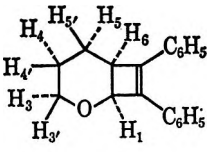
Cyclobutanes are frequently generated in photochemical reactions between olefins. Numerous examples of self-addition as well as cycloaddition between unlike olefins are encountered.[1-3] Reports of cyclobutene formation in the analogous reactions between acetylenes and olefins are confined almost exclusively to the cycloaddition of alkynes to α,β-unsaturated carbonyl compounds,[4-10] most of which require sensitization, although the photocycloaddition reaction between dimethylacetylene dicarboxylate and norbornene has recently been reported.[11] Reports of the participation of arylacetylenes in the photochemical synthesis of cyclobutenes are rare.[10,12]

During the course of our investigation of the photochemical behavior of acetylenes, we found that diphenylacetylene reacted smoothly with an excess of 2,3-dihydropyran to yield a 1:1 addition product upon irradiation at 2537 Å.



I

The product was characterized as the cyclobutene addition product (I), 7,8-diphenyl-2-oxabicyclo[4.2.0]-oct-7-ene, on the basis of spectral evidence presented in the Experimental Section.

An interesting feature of the nmr spectrum was the quartet at τ 6.90 instead of the expected octet. Based on a molecular model, we interpret this to reflect a 90° dihedral angle between H_6–C_6 and H_5–C_5.

In an attempt to gain information regarding the reactive excited species involved in the reaction between diphenylacetylene and 2,3-dihydropyran, quenching and sensitization experiments were performed. It was found that pyrene (triplet energy 48.7 kcal/mol[13]) inhibited the reaction between diphenylacetylene (triplet energy 51 kcal/mol[14]) and 2,3-dihydropyran. Equimolar concentrations of diphenylacetylene and quencher were used. Since their molar extinction coefficients are approximately equal at the excitation wavelength (log ε 4.1 at 2537 Å) the quenching effect was due to triplet energy transfer rather than absorption of the exciting light by pyrene. On the other hand, the reaction conducted in a pyrex vessel and irradiated at 3400 Å was successfully sensitized by triphenylene (triplet energy 66.6 kcal/mol[13]). The unsensitized reaction does not occur upon photolysis at this wavelength. We conclude that the reaction

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(13) W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *ibid.*, **86**, 4537 (1964).
(14) M. Beer, *J. Chem. Phys.*, **25**, 745 (1956).

proceeds through the first excited triplet state of diphenylacetylene.[15]

Experimental Section

The melting point is uncorrected. The nmr spectrum was measured in CCl_4 on a Varian DP-60-IL instrument. The infrared spectrum was obtained on a Perkin-Elmer Model 614 spectrophotometer. The uv spectrum was recorded on a Carey Model 11 spectrophotometer.

7,8-Diphenyl-2-oxabicyclo[4.2.0]oct-7-ene.—Diphenylacetylene (2.0 g, 0.11 mol) was dissolved in 80 g (0.98 mol) of 2,3-dihydropyran and irradiated in quartz for 24 hr at 2537 Å in a Rayonet photochemical reactor while exposed to the atmosphere. Only one reaction product and no diphenylacetylene could be detected by glpc after this time. The reaction mixture was freeze dried and the residual syrup was recrystallized from a methanol–water solution to give 2.12 g (81.5% based on reacted diphenylacetylene) of a white crystalline 1:1 adduct: mp 56–58°; ir (CCl_4), 3040 (aromatic C—H), 2920 (aliphatic C—H), 1585 (aromatic C=C), and 1100 cm^{-1} (C—O—C); uv (cyclohexane), λ_{max} 298 mμ; nmr (CCl_4), τ 2.75 (10 H, multiplet, aromatic protons), 5.40 (1 H, doublet, $J_{1,6}$ = 4.5 cps, H_1), 6.24 (2 H, multiplet, H_3 and $H_{3'}$), 6.90 (1 H, quartet, $J_{5',6}$ = 10.5 cps, H_6), and 8.40 (4 H, multiplet, H_4, $H_{4'}$, H_5, and $H_{5'}$).

Anal. Calcd for $C_{19}H_{18}O$: C, 86.43; H, 6.91. Found: C, 86.05; H, 7.07.

Registry No.—Diphenylacetylene, 501-65-5; 2,3-dihydropyran, 110-87-2; I, 15895-76-8.

(15) There is evidence that the presence of oxygen is required for efficient generation of the triplet state of diphenylacetylene in the absence of sensitizer. See R. C. Henson and E. D. Owen, *Chem. Commun.*, 153 (1967).

The Synthesis of 2- and 4-Bromoestradiol[1]

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Since the 2 and 4 isomers of bromoestradiol (2- and 4-bromo-1,3,5(10)-estratriene-3,17β-diol) were of interest in the cancer program of the Cancer Chemotherapy National Service Center of the National Institutes of Health,[1] they were synthesized in this laboratory. The identity and purity of 4-bromoestradiol is of more than usual importance since it has served as a standard for analyses of microquantities of steroids in biological materials and as a model for X-ray crystallographic studies for Fourier analyses.[2,3] These latter data have, in turn, been used for the elucidation of structures such as that of the plant estrogen mirestrol,[4] as well as for calculations of electronic charge densities related to studies of interactions between steroids and proteins in biological systems.[5,6]

Slaunwhite and Neely[2] have reported methods for the selective preparation of the 2- or 4-bromo isomers of estrone and estradiol with bromine in the presence of iron powder in high yields (75–90%) and purity. We were unable to confirm these results and repeatedly obtained intractable mixtures from which only minor amounts of monobromo isomers were isolated. The formation of the 2 isomer is described by these authors as particularly sensitive to subtle factors, such as the source of the bromine used, etc.[7] They also prepared 4-bromoestradiol by an alternate method in 85% yield, treating estradiol with N-bromosuccinimide in refluxing carbon tetrachloride. In our hands only 7.5% was thus obtained and our physical constants differed greatly from theirs. Subsequently we used the procedure described below, obtaining yields of 25–40% of pure 4-bromoestradiol by treating estradiol with an equimolar amount of N-bromoacetamide in ethanol at 25°. These conditions correspond to those used by Woodward[8] or by Schwenk and coworkers[9] for the preparation of 2,4-dibromestradiol or 4-bromoestrone, respectively. However, no 2-bromo isomers were isolated by these authors, a point stressed by Schwenk and coworkers. From consideration of electronic and steric effects there is, on the balance, no obvious reason for such discrimination, if this is an electrophilic substitution reaction by a bromonium ion. This is illustrated by the fact that nitration of estrone with nitric acid give about equal yields of the 2- and the 4-nitroestrone (37 and 40%, respectively).[10] We therefore carefully examined the mother liquor from the preparation of the 4-bromoestradiol for the presence of the 2 isomer. Guided by thin layer chromatography a product was isolated which upon purification proved to be the 2-bromoestradiol, although its physical characteristics differed markedly from those reported before.[2] Chromatography of its diacetate (V) and fractional precipitation from a solution of its sodium salt removed a very persistent impurity (2,4-dibromoestradiol). The final yield of analytically pure 2-bromoestradiol was usually only about 5.5%, primarily because of high losses during the purification procedure. The 4-bromo isomer was more easily separated, owing to its relatively low solubility, in yields of 25–40%. The indications are, judging from crude yields, thin layer chromatograms and nuclear magnetic resonance data, that in fact the 2 and the 4 isomer are formed in an almost equal ratio (about 3:4). Thus, at least in this particular halogenation of a phenolic steroid no *ortho* position appears to be preferred over the other, contrary to earlier reports.[9]

As mentioned briefly there are substantial differences between our physical data and earlier ones,[2] in fact some identities are clearly in doubt.[11] The various

(1) Supported by Contract No. PH-43-62-479, Cancer Chemotherapy National Service Center, National Institutes of Health, U. S. Public Health Service.

(2) W. R. Slaunwhite and L. Neely, *J. Org. Chem.*, **27**, 1749 (1962).

(3) D. A. Norton, G. N. Kartha, and C. T. Lu, *Acta Cryst.*, **16**, 89 (1963); **17**, 77 (1964); also *Biophys. J.*, **5**, 425 (1965).

(4) N. E. Taylor, D. Crowfoot Hodgkin, and J. S. Rollett, *J. Chem. Soc.*, 3685 (1960).

(5) K. Saudaram and R. K. Mishra, *Biochem. Biophys. Acta*, **94**, 601 (1965).

(6) Both 2- and 4-bromoestradiol were found inactive in estrogen and antiimplantation tests performed in the laboratories of Drs. J. R. Brooks and D. J. Patanelli of the Merck Institute for Therapeutic Research, Rahway, N. J. Such negations of hormonal activities are interesting and possibly of value in the field of cancer. No information has as yet been received by us from the National Institute of Health.

(7) We tried in vain various brands of bromine since the one used by the authors was no longer available. Electrolytically reduced "Iron, Reagent, Powder" from Matheson Coleman and Bell was used by us, the quality and dispersion of which could influence the results.

(8) R. B. Woodward, *J. Amer. Chem. Soc.*, **62**, 1625 (1940).

(9) E. Schwenk, C. C. Castle, and E. Joachim, *J. Org. Chem.*, **28**, 136 (1963).

(10) T. Utne, R. B. Jobson, and R. D. Babson, *ibid.*, in press.

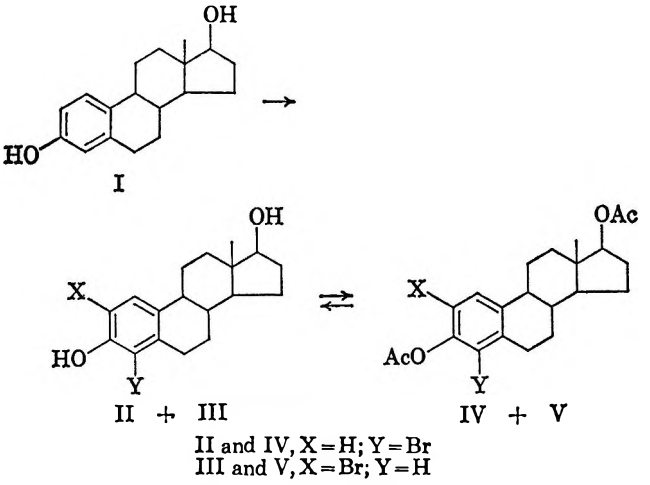
(11) A recent example of a difference between molecular bromine and N-bromoacetamide in aromatic substitution reactions as to isomers formed has been presented by S. Gronowitz, N. Gjös, R. M. Kellog, and H. Wynberg, *ibid.*, **32**, 463 (1967).

TABLE I

	Mp, °C	$[\alpha]^{25}D$, deg	λ_{max}, mμ	ε
2-Bromoestradiol (III)				
Ref 12	197–198	+104	287 (292)	3440 (3230)
Ref 2	156–157	+132	281	2320
Diacetate (V)				
Ref 12	166–168	+41	282.5, 275	1490, 1270
Ref 2	162–163	+109	269	530
4-Bromoestradiol (II)				
Ref 12	213.5–215	+43	283, 288	2220, 2200
Ref 2	207–208	+129	283	2240
Diacetate (IV)				
Ref 12	175.5–177.5	+25	269, 277	466, 440
Ref 2	143–144	+103	275	1280
4-Bromoestrone				
Ref 2	264–265	+136	281	2170
Ref 9	281–283	+147	282, 299	2234, 2340
2,4-Dibromoestrone				
Ref 2	225–226	+133	291 (285)	2800
Ref 9	235–237	+63	285, 293	2900, 3206
2,4-Dibromoestradiol				
Ref 2	218–219	+122	291 (286)	2850
Ref 12	223–226	+66	292 (287)	2800

constants are summarized in Table I,[2,9,12] together with some pertinent data from the literature, which seem to support our values. Of particular note are the differences in melting points and ultraviolet intensities for the 2-bromoestradiol and the strong additional ultraviolet maximum for the 4-bromoestradiol (at 288 mμ) as well as the large differences in optical rotations (up to as much as 86°). Our bromo isomers were both inert toward alcoholic silver nitrate at 25° over 2 days and toward alcoholic potassium hydroxide at 25° for 3 hr, indicating that the bromine atoms were indeed on the aromatic ring.[8] Elsewhere[10] it has been pointed out that in a series of 2- and 4-substituted 1,3,5(10)-estratrienes the ultraviolet absorption intensities enable a facile differentiation of the isomers, since those of the 2 isomers were consistently higher than those of the 4 isomers, mostly by a factor of two to four. As seen above this is also the case for our 2- and 4-bromoestradiol, although the ratio of intensities at 1.56 is somewhat lower than usual, whereas for the corresponding diacetates the ratio is 2.9. Previously equal intensities were reported[2] for these isomers (ratio 1.04), whereas for the diacetates the ratio was actually reversed (0.41). Ultraviolet data similar to ours were found for small samples prepared *via* a Sandmeyer reaction on the 2- and the 4-aminoestrone methyl ether,[2,13,14] followed by cleavage of the ether and sodium borohydride reduction of the ketone. This longer route was less suited for preparative work owing to the small over-all yields.

Despite these unexplainable differences, we believe that our products are pure and of the assigned structures, based on data from thin layer chromatography, phase solubility analyses, nuclear magnetic resonance data, infrared or ultraviolet spectra, elemental analyses, and chemical behavior. (Vapor phase chromatography failed to separate the 2- and 4-bromo isomers.) The nmr spectra clearly indicate the structures to be as formulated below. In one case a quartet centered at τ 2.82 (J = 8.8 cps) is attributed to the *ortho* protons of the 4-bromoestradiol (II), whereas a pair of singlets



at 2.39 and 2.97, without discernible splitting of the *para* protons, is consistent with the 2-bromoestradiol (III) structure.

Experimental Section

Melting points were taken on a calibrated Thomas–Hoover Unimelt apparatus. Ultraviolet spectra were run on a Cary 11 spectrophotometer, infrared spectra were run on a Perkin-Elmer 421 grating spectrophotometer, and nmr spectra were determined on a Varian A-60 spectrometer. Chemical shifts are reported in τ values relative to tetramethylsilane. Optical rotations were measured on a Zeiss photoelectic precision polarimeter.

4-Bromoestradiol (II).—Pure N-bromoacetamide (recrystallized from chloroform–hexane) (20 g, 0.145 mol) was added in portions over 1 hr at 25° to a stirred solution of 40 g of estradiol (I, 0.147 mol) in 2 l. of ethanol dried over molecular sieves. A crystalline material was filtered off after 3 hr and the mother liquor chilled to 0° to give a total of 25 g of crude 4-bromoestradiol. A solution of this product in 500 ml of hot chloroform was poured onto a 900-g silica gel column (Baker). After cooling, elution with chloroform gave 20.6 g (40%), mp 211–215.5°, of essentially pure material. Two recrystallizations from methanol yielded 13.2 g (25.6%) of analytically pure 4-bromoestradiol (II): mp 213.5–215° (lit.[2] mp 207–208°); $[\alpha]^{25}D$ +43° (1%, chloroform) (lit.[2] +129°).[15] Thin layer chromatography (silica gel–chloroform with 5% acetonitrile) showed a single spot (R_f 0.30), and phase solubility analysis indicated 100% purity. Ultraviolet absorptions were at λ_{max}^{MeOH} 283 mμ (ε 2220) [lit.[2] 283 mμ (ε 2240)] and 288 mμ (ε 2200) (lit.[2] none reported).[15,16] The infrared spectrum (in Nujol) exhibited bands at 3200 and 3540 (HO), and 1600 and 1560 cm^{-1} (Ph). The nmr spectrum (in deuteriopyridine) was consistent with the *ortho* proton structure, with a quartet centered at τ 2.82 (J = 8.8 cps) and a singlet at 9.03 (18-CH_3).

Anal.[17] Calcd for $C_{18}H_{23}O_2Br$ (351.3): C, 61.54; H, 6.60; Br, 22.75. Found: C, 61.40; H, 6.58; Br, 22.46.

Treatment of the 4-bromoestradiol (II) with pyridine and acetic anhydride at 25° gave the 4-bromoestradiol diacetate (IV): mp 175.5–177.5° (lit.[2] mp 143–144°); λ_{max}^{MeOH} 269 and 277 mμ (ε 466 and 440) [lit.[2] 275 mμ (ε 1280)]; $[\alpha]D$ +25° (1%, chloroform) (lit.[2] +103°). A hydrolytic acetyl determination confirmed the presence of two acetate groups.

2-Bromoestradiol (III).—By concentration of the mother liquor from the separation of the 4 isomer to a volume of 250 ml solids weighing 16 g separated overnight. Chromatography of these on 400 g of silica gel (Baker) on elution with chloroform with 2% acetonitrile gave 12 g of solids, which were acetylated overnight at 25° in a mixture of 120 ml of dry pyridine and 120 ml of acetic anhydride. Addition of ice water gave a solid which was recrystallized twice from ethanol to give 7.3 g of 2-bromoestradiol diacetate (V): mp 166–168° (lit.[2] mp 162–163°); $[\alpha]^{25}D$ +41°

(12) Prepared by us according to Woodward.[8]
(13) A. J. Tomson and J. P. Horwitz, *J. Org. Chem.*, **24**, 2056 (1959).
(14) S. Kraychy and T. F. Gallagher, *J. Biol. Chem.*, **229**, 519 (1957).
(15) Further recrystallizations from methanol did not alter the physical data given. As to discrepancies with literature values please see text.
(16) Small amounts of 2- and 4-bromoestradiol prepared *via* a Sandmeyer reaction on the aminoestrone methyl ethers showed ultraviolet data similar to ours.
(17) All analytical samples were dried at 95° (0.1 mm) for 20 hr.

(1%, chloroform) (lit.[2] +109°); λ_{max}^{MeOH} 282.5 and 275 mμ (ε 1490 and 1270) [lit.[2] 269 mμ (ε 530)]. Hydrolysis by stirring the suspended diacetate in 70 ml of methanol with 37 ml of a 10% aqueous potassium hydroxide solution at 25° gave a clear solution overnight, which was acidified (pH = 6) and diluted with 65 ml of water. The methanol was removed under vacuum, the suspension was chilled, and the solids were recrystallized from ethanol to yield 4.5 g of crystals, mp 197–198°, in which a small impurity (2,4-dibromoestradiol, R_f 0.39) was still present. The material was dissolved in 90 ml of ethanol, basified with 0.8 g of potassium hydroxide in 3 ml of water, and diluted with 90 ml of water. Fractional precipitation by the cautious addition of 12.5 ml of 1 *N* hydrochloric acid in five equal increments with vigorous stirring gave five crops of material. Three of these, samples 2, 3, and 4, were recrystallized from ethanol to give 2.8 g (5.5%) of analytically pure 2-bromoestradiol (III): mp 197–198° (lit.[2] 156–157°); $[\alpha]^{25}D$ +104° (1%, chloroform) (lit.[2] +132°).[15] Thin layer chromatography (silica gel–chloroform with 5% acetonitrile) showed a single spot (R_f 0.34); vapor phase chromatography exhibited a single peak. Ultraviolet absorptions were at λ_{max}^{MeOH} 287 mμ (ε 3440), shoulder at 292 mμ (ε 3230) [lit.[2] 281 mμ (ε 2320)].[15,16] The infrared spectrum (in Nujol) exhibited bands at 3620, 3590, and 3260 (OH) and 1600, 1560, and 1480 cm^{-1} (Ph). The nmr spectrum (in deuteriopyridine) was consistent with the assigned structure, showing no discernible splitting of the *para* protons and a pair of singlets at τ 2.39 and 2.97 and a singlet at 9.13 (18-CH_3).

Anal. Found: C, 61.30; H, 6.71; Br, 22.85 (for calculated values, see above).

Registry No.—II, 1630-83-7; III, 15833-07-5; IV, 15833-06-4; V, 15856-39-0.

Acknowledgments.—The authors wish to thank Dr. Byron H. Arison for interpretation of the nmr spectra, Mr. Richard N. Boos and his staff for the elemental analyses, Mr. Alec Kalowsky for the ultraviolet spectra, and Mr. Frederick Lostbourne for the optical rotation measurements.

Total Synthesis of *dl*-Sabinene, *dl*-*trans*-Sabinene Hydrate, and Related Monoterpenes

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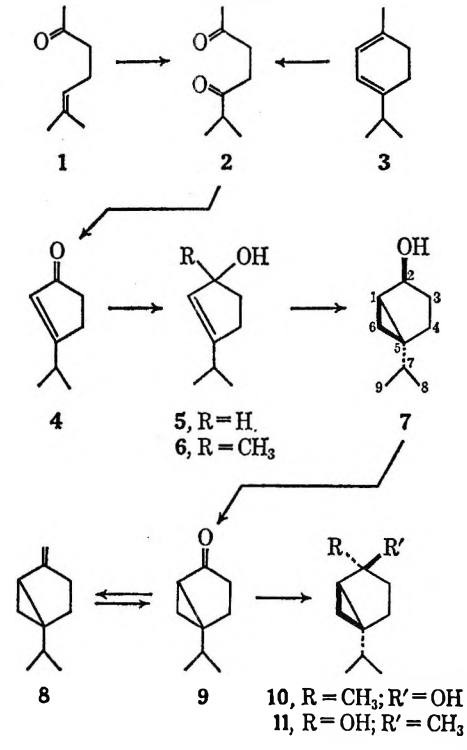
Despite the frequent occurrence of monoterpenes possessing the bicyclo[3.1.0]hexane ring system in essential oils, synthetic approaches to these substances have received little attention. As part of an over-all program directed toward the synthesis of mono- and sesquiterpenes, we investigated the construction of several representative bicyclo[3.1.0]hexanes of the sabinane group: sabinene (**8**),[1,2] sabina ketone (**9**),[3] and *cis*- and *trans*-sabinene hydrates (**10** and **11**).[4,5] Sabinene is reported to be present in a wide variety of essential oils including savin oil,[6] lavandin oil,[7] *Juniperus horizontalis* leaf oil,[8] and citrus oils[9] while sabina ketone is reportedly present in lavandin oil.[10] Although *cis*-sabinene hydrate has not been found in nature, the *trans* isomer represents a small but very important part of a number of mint oils.[5,11–13]

Although Eastman and coworkers[5] have reported the preparation of *cis*- and *trans*-sabinene hydrates from naturally occurring sabinene, no total syntheses of any of these materials has come to our attention.[13a] We wish to report here the total syntheses of racemic counterparts of the aforementioned members (**8**–**11**) of the sabinane group.

Our initial synthetic objective was *cis*-sabinene hydrate (**10**). Several reports, including an extensive investigation by Dauben and Berezin,[14] note that allylic and homoallylic alcohols react with the Simmons–Smith reagent[15] *via* participation of the hydroxyl function. This interaction results in a product having the alcohol function and the newly generated cyclopropyl ring in a *cis* relationship to one another. With this fact in mind, a synthetic scheme which is quite stereoselective can be visualized along lines outlined in Chart I.

CHART I



The required starting dione 2 was available by either of two procedures. The readily available 2-methyl-2-hepten-6-one (1) was hydroborated with 2 equiv of

(1) J. L. Simonsen, "The Terpenes," Vol. II, 2nd ed, University Press, Cambridge, England, 1949, pp 16–23, and references therein.

(2) E. Guenther, "The Essential Oils," Vol. II, D. Van Nostrand Co., New York, N. Y., 1949, pp 64–65, and references therein.

(3) A. G. Short and J. Read, *J. Chem. Soc.*, 1415 (1939).

(4) O. Wallach, *Ann.*, **357**, 65 (1907); **360**, 82 (1908).

(5) J. W. Daly, F. C. Green, and R. H. Eastman, *J. Amer. Chem. Soc.*, **80**, 6330 (1958).

(6) A. B. Booth, *Amer. Perfumer Aromat.*, **69**, 45 (1957); *Chem. Abstr.*, **51**, 7658 (1957).

(7) I. Calvarno, *Essenze Deriv. Agrumari*, **34**, 169 (1964); *Chem. Abstr.*, **63**, 5443 (1965).

(8) F. M. Couchman and E. von Rudloff, *Can. J. Chem.*, **43**, 1017 (1965).

(9) R. M. Ikeda, W. L. Stanley, L. A. Rolle, and S. H. Vannier, *J. Food Sci.*, **27**, 593 (1962); *Chem. Abstr.*, **60**, 7371 (1964).

(10) P. A. Stadler, *Helv. Chim. Acta*, **43**, 1601 (1960).

(11) K. L. Handa, D. M. Smith, I. C. Nigam, and L. Levi, *J. Pharm. Sci.*, **53**, 1407 (1964).

(12) E. von Rudloff and F. W. Hefendehl, *Can. J. Chem.*, **44**, 2015 (1966).

(13) I. C. Nigam and L. Levi, *J. Agr. Food Chem.*, **11**, 276 (1963).

(13a) NOTE ADDED IN PROOF.—Since submission of this manuscript, a total synthesis of sabina ketone and sabinene by a different route has been reported: M. Marx, Ph.D. Thesis, Columbia University, New York, N. Y., 1966; *Dissertation Abstr.*, **27**, 4266-B (1967).

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

(15) H. E. Simmons and R. D. Smith, *ibid.*, **81**, 4256 (1959).

diborane in tetrahydrofuran and the resultant alkylborane was oxidized with alkaline hydrogen peroxide. Oxidation of the crude diol with chromic acid reagent[16] afforded dione **2** in 90% yield. Alternately, the ketone could be isolated in moderate yield by ozonation of α-terpinene (**3**) and subsequent reductive work-up.

Treatment of **2** with 2% aqueous sodium hydroxide in refluxing ethanol for 4.5 hr afforded cyclopentenone **4** (70%). Addition of ethereal methyllithium to ketone **4** produced the extremely unstable tertiary alcohol **6** which resisted attempts at purification: λ_{max}^{film} 2.95 μ; nmr signals at τ 4.79 (C=CH), 8.72 ($HOCCH_3$), 8.95 (doublet, J = 7 Hz, $CHCH_3$). The crude alcohol, when subjected to a Simmons–Smith reaction, decomposed rapidly and no bicyclic product (*e.g.*, **10** or **11**) could be isolated. On the other hand, reduction of cyclopentenone **4** with lithium aluminum hydride in ether at room temperature afforded the more stable secondary alcohol **5** (90%). This substance reacted rapidly with the zinc–copper couple and methylene iodide to afford demethyl-*cis*-sabinene hydrate (**7**) as a woody, camphoraceous-smelling oil. This bicyclic material was oxidized smoothly with chromic acid reagent to sabina ketone (**9**) in 90% yield. An authentic sample of the green, leafy-smelling sabina ketone, prepared by the oxidation of sabinene[17] (**8** → **9**) exhibited nmr and infrared spectral data as well as gas chromatographic retention time identical with those of the synthetic material.

Synthetic sabinene (**8**) was prepared by treatment of sabina ketone (**9**) with methylene triphenyl phosphorane in dimethyl sulfoxide. The crude oil was purified by filtration through a Florisil column and evaporative distillation. An authentic sabinene sample[17] exhibited spectral data and gas chromatographic retention time identical with those of the synthetically prepared material.

The final two objectives of the synthetic scheme were realized by treatment of sabina ketone (**9**) with ethereal methyllithium. This process afforded a mixture containing predominantly the two alcohols **10** and **11** in a ratio of about 8:1, respectively (90% yield). The use of methylmagnesium bromide[5] in place of methyllithium gave substantial increases in bicyclic ring decomposition. The two tertiary alcohols were separated by gas chromatography. Pure *cis*-sabinene hydrate, as described by Eastman,[18] exhibited spectra identical with those recorded for the major component of this mixture. In addition, pure *trans* isomer, as described by Eastman,[18] exhibited spectra identical with those prepared from the minty-smelling synthetic material. The gas chromatographic retention time of synthetic *trans*-sabinene hydrate was identical with those of a sample isolated from native spearmint and a sample generously donated by Dragoco Chemical Co.

Experimental Section[19]

2-Methyl-3,6-heptanedione (2). A. From 2-Methyl-2-hepten-6-one (1).—A solution of 50.4 g (0.4 mol) of **1** in 300 ml of tetrahydrofuran maintained at 0–5° was treated with 400 ml (0.4 mol) of 1 *M* diborane solution (Ventron Corp., Beverly, Mass.) over 1 hr.[19b] The resulting solution was stirred at 0–5° for 1 hr and at 25–27° for 3.5 hr, then cooled in an ice bath, and treated cautiously with 80 ml of water. With the temperature maintained at 0–5°, 200 ml of 3 *N* aqueous sodium hydroxide was added followed by 200 ml of 30% hydrogen peroxide over 30 min. The reaction was stirred at 0–5° for an additional 1 hr and at 25–27° overnight. Isolation[19f] afforded 82.8 g of crude diol (containing solvent) which was dissolved in 300 ml of acetone, cooled to 0–5°, and treated with 240 ml of Jones reagent[16] over 1 hr. The mixture was stirred an additional 1.75 hr prior to addition of 25 ml of isopropyl alcohol. Combined ether extracts were washed with several portions of saturated aqueous sodium bicarbonate which were back extracted and the total ether was washed with brine and dried. Solvent removal and subsequent distillation afforded 51.6 g (91%) of dione **2**, bp 68–72° (4.5 mm), which was shown to be 95% pure by glpc (150°). Material purified by redistillation and gas chromatography (150°) exhibited the following properties: bp 71–72° (5 mm); $n^{25}D$ 1.4250 [lit.[20] bp 79–82° (9 mm); $n^{20}D$ 1.4322]; λ_{max}^{film} 5.86, 8.60, 9.19, and 9.80 μ; nmr signals at τ 7.46 (5 H), 7.94 (3 H, $COCH_3$), and 8.95 (6 H, doublet, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.8; H, 10.2.

B. From α-Terpinene.—A stream of ozone–oxygen was bubbled through a solution of 17.17 g of a mixture of α- and γ-terpinene[21] [containing 11.5 g (0.085 mol) of α-terpinene] in 250 ml of methanol maintained at −78° over 5 hr. The cold ozonide solution was slowly added to a mixture of 140 g of sodium iodide and 72 ml of acetic acid in 200 ml of methanol and stirred overnight at room temperature. The resulting dark solution was decolorized with solid sodium bisulfite and neutralized with solid sodium bicarbonate. Isolation[19f] and distillation afforded 9.95 g (83% based on α-terpinene) of dione **2**, bp 70–72° (5.2 mm), which was shown to be 89% pure by glpc (150°).

3-Isopropyl-2-cyclopentenone (4).—A solution of 51.6 g (0.36 mol) of dione **2** in 580 ml of 2% aqueous sodium hydroxide and 180 ml of ethanol was refluxed under nitrogen[19b] for 4.5 hr. Isolation[19f] and subsequent distillation afforded 32.2 g (71%) of ketone **4**, bp 62–64° (2.75 mm) which showed greater than 95% purity by glpc (150°). Material purified by redistillation and glpc (150°) exhibited these properties: bp 73–74° (4.75 mm); $n^{25}D$ 1.4774; λ_{max}^{film} 5.84, 6.20, 7.95, 8.50, 10.15, and 11.62 μ; λ_{max}^{EtOH} 228 mμ (ε 12,500); nmr signals at τ 4.25 (1 H, C=CH), 7.25–7.60 (3 H), 7.65–7.89 (2 H), and 8.85 (6 H, doublet, J = 7 Hz, $CHCH_3$) [lit.[22] for ketone **4**: bp 75–76° (3 mm); $n^{15}D$ 1.4850; λ_{max}^{film} 5.85 and 6.19 μ; λ_{max}^{EtOH} 226.5 mμ (ε 13,750); nmr signals at τ 4.22 (1 H), 7.2–7.8 (4 H), and 8.83 (6 H)].

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.2; H, 9.8.

3-Isopropyl-2-cyclopentenol (5).—A solution of 32.2 g (0.26 mol) of ketone **4** in 100 ml of anhydrous ether was added over 15 min to a rapidly stirring, ice cold slurry of 5.0 g (0.13 mol) of lithium aluminum hydride in 500 ml of ether. The resulting mixture was stirred at room temperature for 2 hr and was decomposed by the cautious dropwise addition of 10 ml of water

(16) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(17) Fluka Chemical Co. supplies sabinene which is only *ca.* 67% pure.

(18) Reference 2, footnote 1.

(19) (a) The prefix *dl* is omitted from the names of racemic substances. (b) The apparatus described by W. S. Johnson and W. P. Schneider [*Org. Syn.*, **30**, 18 (1950)] was used to maintain a nitrogen atmosphere. (c) Infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer; ultraviolet spectra were determined in ethanol on a Perkin-Elmer Model 202 spectrophotometer; nmr spectra were determined in carbon tetrachloride [chemical shifts measured relative to tetramethylsilane (τ 10)] with a Varian Model HA-100 spectrometer by T. J. Flautt and associates of these laboratories; gas–liquid partition chromatography was accomplished with an Aerograph Model 202B using a flow rate of 100 cc/min on a 5 ft × 0.25 in. 20% FFAP on 60/80 Chromosorb P column at the temperature indicated. (d) Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. (e) Anhydrous tetrahydrofuran was obtained by distillation from lithium aluminum hydride; anhydrous dimethyl sulfoxide was obtained by distillation from calcium hydride. (f) The isolation procedure consisted of thorough extraction with ether, washing the combined extracts with brine solution, and drying over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a hot water bath.

(20) (a) C. G. Moore, *J. Chem. Soc.*, 234 (1951); (b) K. von Auwers and R. Hinterseber, *Ber.*, **48**, 1357 (1915).

(21) Prepared by potassium *t*-butoxide–dimethyl sulfoxide room temperature isomerization of γ-terpinene (prepared by lithium ammonia reduction of *p*-cymene).

(22) (a) L. Crombie and D. A. Mitchard, *J. Chem. Soc.*, 5640 (1964). (b) O. L. Chapman, T. A. Rettig, A. A. Griswold, A. I. Dutton, and P. Fitton, *Tetrahedron Lett.*, **29**, 2049 (1963).

and 8 ml of 10% aqueous sodium hydroxide. The reaction mixture was stirred overnight and filtered, and the solvent was removed at reduced pressure to afford 31.8 g (97%) of cyclopentenol **5**. Material purified by distillation exhibited these properties: bp 65–67° (3.5 mm); n^{25}D 1.4658; λ_{max}^{film} 3.00, 6.08, 9.71, 10.29, and 11.75 μ; nmr signals at τ 4.68 (1 H, C=CH), 5.36 (1 H, CHOH), 5.95 (1 H, OH), and 8.97 (6 H, doublet, J = 7 Hz, $CHCH_3$). Because the material was only moderately stable and decomposed on storage after several days, it was converted directly into bicyclic alcohol **7** without analysis.

Demethyl-*cis*-sabinene Hydrate (7).—An adaptation of the procedure of Dauben and Berezin[14] was employed. A nitrogen blanketed[19b] slurry of 7.84 g (0.12 mol) of zinc–copper couple[23] and a crystal of iodine in 60 ml of anhydrous ether was treated rapidly with 26.4 g (0.1 mol, 8 ml) of freshly distilled methylene iodide. The rapidly stirred mixture was heated at 40° for 0.5 hr. A solution of 6.42 g (0.05 mol) of pentenol **5** in 16 ml of ether was added dropwise at a rate sufficient to maintain gentle reflux without external heat (*ca.* 0.5 hr). Following addition, the reaction was refluxed for 1 hr, cooled, treated cautiously with excess saturated, aqueous ammonium chloride, and filtered. The solid was washed well with ether and the resulting filtrate was washed with two portions of 10% aqueous sodium carbonate. The combined aqueous layers were back extracted, and the combined ether layers were washed with brine and dried over magnesium sulfate. Solvent removal and subsequent distillation afforded three fractions: (1) 0.45 g, bp 25–40° (1 mm), containing 9% alcohol **7** by glpc (150°); (2) 0.34 g, bp 40–56° (1 mm), containing 75% alcohol **7**; (3) 4.62 g (66%) bp 56–57° (1 mm), containing 95% alcohol **7**. This material was purified by distillation, bp 60° (1 mm), and glpc (150°): n^{25}D 1.4655; λ_{max}^{film} 3.00, 9.49, and 9.75 μ; nmr signals at τ 5.55 (1 H, multiplet, CHOH), 7.90 (1 H, OH), 9.08 (3 H, doublet, J = 6 Hz, $CHCH_3$), 9.14 (3 H, doublet, J = 6.5 Hz, $CHCH_3$), 9.32 [1 H, triplet, J(C-6-*endo* H, C-1 H) = 4.5 Hz, J(C-6-*endo* H, C-6-*exo* H) = 4.5 Hz, C-6-*endo* H], and 9.69 [1 H, quartet, J(C-6-*exo* H, C-1 H) = 7.7 Hz, J(C-6-*endo* H, C-6-*exo* H) = 4.5 Hz, C-6-*exo* H].[24,25]

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.9; H, 11.6.

Sabina Ketone (9).—A solution of 4.62 g (0.033 mol) of alcohol **7** in 75 ml of acetone maintained at 0–5° was oxidized with 9 ml of Jones reagent[16] over a 15-min period. The resulting solution was stirred an additional 10 min at 0–5° and added to brine. Several ether extracts were washed with saturated aqueous sodium bicarbonate, the aqueous layers were back extracted, and the total ether was washed with brine and dried over magnesium sulfate. Removal of the solvent and distillation afforded 4.05 g (89%) of faint yellow sabina ketone, bp 67–70° (5 mm), n^{25}D 1.4654 (lit.[3] n^{25}D 1.4672), which showed 96% purity by glpc (150°). Pure material obtained by redistillation, bp 70° (5 mm), and glpc (150°) collection exhibited these spectral properties: λ_{max}^{film} 3.30, 5.79, 8.49, 9.79, 10.93, and 12.86 μ; nmr signals at τ 7.70–8.16 (3 H), 8.25–8.70 (2 H), and 8.73–9.20 (9 H). A pure sample of sabina ketone prepared by ozonation of naturally occurring sabinene[17] had an index of refraction of n^{25}D 1.4645 and an infrared spectrum superimposable with the synthetic material.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.4; H, 10.3.

Sabinene (8).—A slurry of 1.24 g (0.032 mol) of a 61% sodium hydride–mineral oil dispersion in 40 ml of dimethyl sulfoxide was heated at 70° under nitrogen[19b] for 1 hr. The resulting base solution was cooled to 0–5° and treated with a warm solution of 11.9 g (0.033 mol) of methyltriphenylphosphonium bromide in 40 ml of dimethyl sulfoxide. The semisolid mixture slowly warmed to 25–27° where solution took place. Stirring was continued for 20 min at 25–27°, and a solution of 1.30 g of 74% pure sabina ketone (0.007 mol) in 20 ml of dimethyl sulfoxide was added dropwise over 5 min. The resulting dark yellow solution was stirred at 25–27° for 3 hr, and added to water, and the product isolated with pentane. Several extracts were combined, washed with water and brine, and dried over magnesium sulfate. The solvent was removed by distillation and the total crude was passed through a chromatographic column containing 100 ml of Florisil. One 300-ml pentane fraction was collected and the pentane removed by distillation to afford 2.9 g of colorless, residual oil which on evaporative distillation afforded 880 mg (93% material balance) of colorless product, bp 60–70° (16 mm), which showed 79% purity by glpc (90°). A sample purified by glpc (90°) had the properties n^{25}D 1.4654 [lit.[26] bp 69° (30 mm), n^{20}D 1.4681]; λ_{max}^{film} 3.29, 6.04, 7.28, 7.37, 9.78, and 11.53 μ; nmr signals at τ 5.27, 5.46 (2 H, C=CH_2), 9.10 (3 H, doublet, J = 6 Hz, $CHCH_3$), 9.18 (3 H, doublet, J = 7 Hz, $CHCH_3$), and 9.34 and 9.40 (2 H, C-6 H's). A purified sample of natural sabinene[17] exhibited superimposable spectra with those reported above.

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.0; H, 11.8.

***cis*- and *trans*-Sabinene Hydrate (10, 11).**—A solution of 2.94 g (0.021 mol) of sabina ketone (88% pure) in 16 ml of ether was added over 10 min to 37 ml of a 1.62 *M* solution of ethereal methyllithium and 26 ml of ether contained under a nitrogen atmosphere.[19b] The resulting mixture was refluxed for 1 hr, cooled, and poured onto excess ice. Isolation[19f] afforded 3.30 g (100% material balance) of faint green oil composed of solvent, an unknown [17% (10% present in starting material)], *trans*-sabinene hydrate (11, 13%), *cis*-sabinene hydrate (10, 71%), and sabina ketone (9, 1%). A run using 97% pure sabina ketone gave 11% *trans*- and 84% *cis*-sabinene hydrate. The crude products were chromatographed on 500 ml of Florisil with glpc (125°) monitoring of fractions. Subsequent combination and distillation afforded 680 mg of a mixture of unknown and isomeric alcohols **10** and **11** and 550 mg of pure *cis*-sabinene hydrate (**10**).

Pure *cis* isomer **10** exhibited the properties which follow: n^{25}D 1.4632; λ_{max}^{film} 3.00, 7.36, 8.85, 9.50, 10.12, 10.51, and 10.78 μ; nmr signals at τ 7.55 (1 H, OH), 8.70 (3 H, $HOCCH_3$), 9.08 (3 H, doublet, J = 6.3 Hz, $CHCH_3$), 9.12 (3 H, doublet, J = 6.5 Hz, $CHCH_3$), 9.34 [1 H, quartet, J(C-6-*endo* H, C-1 H) = 4.0 Hz, J(C-6-*endo* H, C-6-*exo* H) = 4.9 Hz, C-6-*endo* H], and 9.71 [1 H, quartet, J(C-6-*exo* H, C-1 H) = 8.0 Hz, J(C-6-*endo* H, C-6-*exo* H) = 4.9 Hz, C-6-*exo* H].[24,25] Pure *cis*-sabinene hydrate as described by Eastman[18] exhibited spectra identical with those described above.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.7; H, 11.8.

Pure *trans*-sabinene hydrate (**11**) exhibited these spectral properties: $\lambda_{max}^{CCl_4}$ 2.80, 2.90, 7.23, 8.46, 9.46, 9.71, 10.03, 10.34, 10.86, and 10.99 μ; nmr signals at τ 8.70 (3 H, $HOCCH_3$), 9.03 (3 H, doublet, J = 7 Hz, $CHCH_3$), 9.10 (3 H, doublet, J = 7.5 Hz, $CHCH_3$), 9.62 [1 H, quartet, J(C-6-*exo* H, C-1 H) = 8.1 Hz, J(C-6-*endo* H, C-6-*exo* H) = 5.0 Hz, C-6-*exo* H], and 9.80 [1 H, triplet, J(C-6-*endo* H, C-1 H) = 5.0 Hz, J(C-6-*endo* H, C-6-*exo* H) = 5.0 Hz, C-6 H (*endo*)].[24,25] Pure *trans* isomer as described by Eastman[18] exhibited spectra identical with those described above. Glpc retention time (125°) of the synthetic **11** was identical with those of a sample obtained from native spearmint and to a sample obtained from Dragoco Chemical Co.

Registry No.—**2**, 13901-85-4; **4**, 1619-28-9; **5**, 15826-78-5; **7**, 15826-79-6; **8**, 15826-80-9; **9**, 513-20-2; **10**, 15826-82-1; **11**, 15826-83-2.

Acknowledgments.—The technical assistance of Mr. Kerry M. Fitzpatrick on part of this work is gratefully acknowledged.

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

(24) See W. G. Dauben and W. T. Wipke, *J. Org. Chem.*, **32**, 2976 (1967), for a discussion of nmr spectra of related bicyclic compounds.

(25) IUC nomenclature has been employed, see structure **7**.

(26) G. Ohloff, G. Uhde, A. F. Thomas, and E. sz. Kováts, *Tetrahedron*, **22**, 309 (1966).

The Reactions of Fluoroaromatic Nitriles with Sodium Pentafluorophenolate

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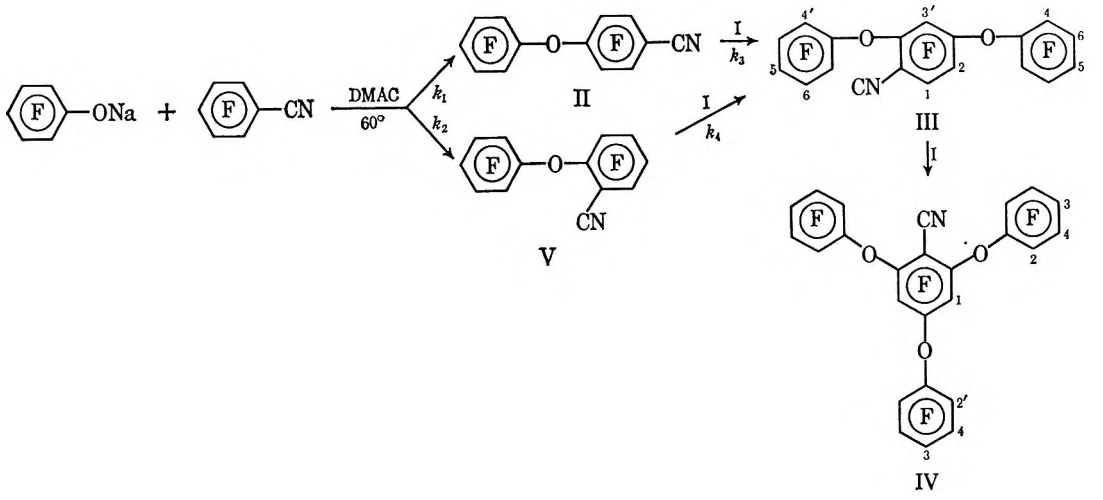
Sodium pentafluorophenolate (I) reacts with a series of substituted pentafluorobenzenes in dimethylacetamide (DMAC) yielding 4-substituted nonafluorodi-

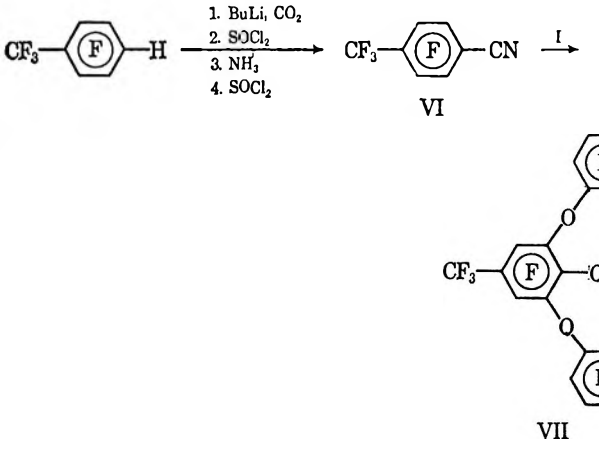


phenyl ethers.[1] In our continuing studies on the synthesis and reactions of perfluorodiphenyl ethers we have observed that I reacts with pentafluorobenzonitrile[2] to yield either mono- and/or polysubstituted products.

4-Cyanononafluorodiphenyl ether (II) was synthesized in an 82% yield through the reaction between I and pentafluorobenzonitrile in an acetone medium (25°). In DMAC as a solvent (70°), an unusual abundance of isomeric and polysubstituted products accompanied the formation of II. When 2.24 equiv of I was allowed to react with 1 equiv of pentafluorobenzonitrile, two polysubstituted products (III and IV) were isolated. All reactions carried out in this study were monitored by vapor phase chromatographic (vpc) analysis. As the reaction proceeded, the concentration of II and another product V (suspected to be the *ortho* isomer) steadily increased and then diminished with further reaction time. Their ratio (II:V, 10:1) was relatively constant during the initial stages of the reaction. However, as the product III began to appear, this ratio became progressively larger implying that V was consumed faster than II. These observations can be rationalized by considering the following scheme where $k_1 > k_2$ and $k_4 > k_3$.

We have shown in our previous study[1] that in a series of monosubstituted pentafluorobenzenes (C_6F_5X, X = H, F, Cl, Br, C_6F_5, CO_2Et, and CF_3) the CF_3 group was the most activating group towards nucleophilic reactions with I. In order to assess the activating influence of a CN group, a competitive experiment was carried out between pentafluorobenzonitrile and octafluorotoluene for I in DMAC (47°). Analysis of the *p*-perfluorodiphenyl ether products in the reaction mixture demonstrated the greater reactivity of pentafluorobenzonitrile [$k(C_6F_5CN)/k(C_6F_5CF_3) = 39$ (*para*)]. From the ratio of V:II in this experiment, *ortho* substitution on pentafluorobenzonitrile was estimated to be as fast as *para* substitution on octafluorotoluene.

In order to demonstrate the facile displacement of the fluorine atoms *ortho* to a CN group, 4-trifluoromethyltetrafluorobenzonitrile (VI) was synthesized from 4-hydroheptafluorotoluene by conventional methods. The reaction of VI with I gave the expected *ortho* disubstituted product VII.



The activating effect of a CN substituent was further demonstrated by the observation that both pentafluorobenzonitrile and compound III were obtained when II was allowed to react with anhydrous sodium fluoride under stringent reaction conditions (DMAC, 110°, 18 hr). This demonstrates the potential reversibility of the reaction between pentafluorobenzonitrile and I. Our recently reported[1] reactions between I and the less reactive substituted pentafluorobenzenes were irreversible under these experimental conditions in agreement with the relative rate data and the reported mechanistic interpretation. Apparently in the reaction between pentafluorobenzonitrile and I (or the reverse reaction, *e.g.*, II and NaF), the CN group can stabilize the rate-determining transition state to the extent that reversibility is realized.

The observations in this study strongly suggest that a CN substituent is a potent activator for *ortho* and *para* nucleophilic substitution reactions on fluorinated aromatic compounds.

Experimental Section

The fluoroaromatics in this work were purchased from Imperial Smelting Corporation Ltd., Avonmouth, England, and were used without further purification. The DMAC was analytical grade and dried over a molecular sieve (Linde Molecular Sieve 5A) prior to use; all other solvents utilized were analytical grade. Boiling points and melting points are uncorrected.

(1) R. J. De Pasquale and C. Tamborski, *J. Org. Chem.*, **32**, 3163 (1967).

(2) In addition to our study of pentafluorobenzonitrile, recent reports also indicate that a polyfluoroaromatic nitrile undergoes facile *ortho* and *para* nucleophilic substitution reactions. See (a) E. Felstead, H. C. Fielding, and B. J. Wakefield, *J. Chem. Soc. C*, 708 (1966); (b) R. D. Chambers, R. A. Storey, and W. K. R. Musgrave, Fourth International Symposium on Fluorine Chemistry, Estes Park, Colo., July 1967, paper no. 39.

The F^{19} nmr spectra were recorded on a Varian V-4300-2-DP spectrometer at 40 Mcps. Chemical shifts are reported in parts per million (ppm) from external trifluoroacetic acid (TFAA). Acetone was used as the solvent unless otherwise stated. Infrared spectra were run on a Perkin-Elmer Infracord spectrophotometer as KBr pellets or as liquid films. The vapor phase chromatography analysis was done on an F & M Model 500 instrument using a helium flow of 60 cc/min, a 6 ft × 0.25 in. column, 20% Apiezon L on 60–80 mesh Chromosorb W, and programmed from 100–275° (21° per minute) after which it was held at this temperature. The mass spectra were recorded on an AEI MS-9 mass spectrometer.

4-Cyanononafluorodiphenyl Ether (II).—Pentafluorobenzonitrile (20.0 g, 0.104 mol), sodium pentafluorophenolate (10.4 g, 0.0520 mol), and 200 ml of anhydrous acetone were stirred at room temperature under a helium atmosphere. The reaction was followed by periodically withdrawing samples of the reaction mixture and analyzing by vpc. After about 3 days, the reactant (C_6F_5CN) and product peaks remained constant. Less than 2% of side products were present in this crude reaction mixture. The solvent was evaporated and the unreacted pentafluorobenzonitrile was removed by distillation at reduced pressure. The residue was triturated with petroleum ether (30–60°) and filtered to remove 1.7 g of inorganic salts. The filtrate was concentrated and deposited an off-white solid which was recrystallized from methanol–water (40:3) to yield 12.3 g of a white solid, mp 61–62°. Upon further concentration of the mother liquor, 4.8 g of additional solid was obtained. This crude material was dissolved in petroleum ether (30–60°) and eluted from an alumina column with petroleum ether (30–60°). Further recrystallization (methanol–water) yielded 2.8 g of product, mp 59–62° (15.1-g total, 82% yield). A vpc analysis of the combined solids showed less than 1% impurity. The infrared spectrum of II showed a CN band at 4.4 μ. The ^{19}F nmr spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{13}F_9NO$: C, 43.72; F, 47.88; N, 3.92. Found: C, 43.73; F, 47.62; N, 3.95.

Reaction of Pentafluorobenzonitrile with Excess Sodium Pentafluorophenolate.—Pentafluorobenzonitrile (3.27 g, 0.0170 mol) and sodium pentafluorophenolate (7.83 g, 0.0380 mol) were added to DMAC (100 ml) under an atmosphere of nitrogen. The stirred reaction mixture was maintained at 60° for 18 hr, allowed to cool, and filtered to remove the inorganic salts. The filtrate was then added to 300 ml of distilled water, causing a solid to precipitate. The aqueous DMAC solution was decanted; the solid was washed with water and cold methanol. This crude material, 7.9 g, had a melting point range of 130–150°. This solid was then stirred in 80 ml of refluxing hexane and filtered while hot leaving 3.2 g of an insoluble fraction. Recrystallization of this insoluble material from petroleum ether (90–120°) yielded 2.9 g (25%) of a white crystalline solid, mp 184–185°. Structure IV was proposed for this component based on elemental and nmr analysis.

Anal. Calcd for $C_{25}F_{17}O_3N$: C, 43.82; F, 47.14; N, 2.04. Found: C, 43.94; F, 46.85; N, 2.36.

The F^{19} nmr spectrum of IV exhibited a broad singlet at 70.0 ppm (area 2) which on an expanded scale showed five distinct lines with two more (heptet) barely distinguishable. This band was assigned F-1 coupled to F-2 and F-2′. At 74.9 ppm (area 6) was a three-band multiplet (with fine structure) which is believed to be composed of two sets of superimposable doublets, F-2 and F-2′, the former being more deshielded owing to the inductive and anisotropic influences of the cyano group. The remaining absorptions, a distorted triplet (area 3) at 83.4 and a triplet with fine structure (area 6) at 86.4 ppm, were assigned F-3 and F-4, respectively. The experimental coupling constants are $J_{12,12'} \sim 4$; $J_{24} \sim 21$; $J_{34} \sim 21$; and $J_{23,2'3} \sim 3$ cps.

The nmr data indicates that restricted rotation at room temperature appears to be negligible owing to the J_{12} coupling symmetry.

The hexane soluble fraction was concentrated and eluted from a short alumina column with hexane. Concentration of the solvent yielded 3.7 g (41%) of a colorless oil that solidified on standing, mp 70–72° (III).

Anal. Calcd for $C_{19}F_{13}O_2N$: C, 43.78; F, 47.39; N, 2.69. Found: C, 43.89; F, 47.01; N, 2.71.

The F^{19} nmr spectrum of III exhibited a doublet of doublets at 55.6 ppm (area 1) assigned F-1 ($J_{12} \sim 21$; $J_{13} \sim 10$ cps), a doublet of quartets centered at 71.8 ppm (area 1) assigned F-2 ($J_{23,24} \sim 4$ cps), and a broad multiplet (area 1) centered at 76.1 ppm assigned to F-3. The remaining absorptions at 76.9 (area 4), 83.0 (area 2), and 85.8 ppm (area 4) were assigned F-4–F-4′, F-5, and F-6, respectively. Similar with the spectrum of IV, the band at 76.9 ppm consisted of two sets of superimposable doublets.

The infrared spectra of III and IV indicated CN absorptions at 4.44 and 4.49 μ, respectively.

Reaction of 4-Cyanononafluorodiphenyl Ether and Sodium Fluoride.—In an atmosphere of nitrogen, 4-cyanononafluorodiphenyl ether (1.0 g, 2.8 mmol), anhydrous sodium fluoride (0.18 g, 2.8 mmol), and 35 ml of DMAC were heated and stirred at 110° for 18 hr. The reaction mixture was allowed to cool and added to 100 ml of distilled water. The resulting mixture was extracted with three 30-ml portions of methylene chloride. The combined organic extracts were washed three times with 30-ml portions of water, dried over magnesium sulfate, and concentrated, yielding 0.9 g of a solid residue. A vpc analysis of this residue showed that the mixture consisted of three components in the ratio 1:50:2. The components were identified as pentafluorobenzonitrile, 4-cyanononafluorodiphenyl ether (II), and 2,4-bis(pentafluorophenoxy)-3,5,6-trifluorobenzonitrile (III), respectively.

4-Trifluoromethyltetrafluorobenzonitrile (VI).—4-Trifluoromethyltetrafluorobenzoic acid[3] (18.0 g, 0.0680 mol) was added to thionyl chloride (72.8 g, 0.560 mol) containing 0.3 g of dimethylformamide. The solution was heated at reflux temperature for 17 hr. During the first 5 hr, gas evolution was noted. The excess thionyl chloride was removed (water aspirator) and the remaining residue was distilled to yield 16.0 g (84%) of 4-trifluoromethyltetrafluorobenzoyl chloride, bp 70–72° (12 mm). The infrared spectrum of the acid chloride exhibited a C=O band at 5.70 μ.

The acid chloride was added dropwise to a stirred solution of 15 *N* ammonium hydroxide (7.0 g) in 40 ml of THF. During the addition, the temperature of the reaction mixture was maintained at −10 to 0°. At the completion of the reaction, the white precipitate which formed was filtered (NH_4Cl). The filtrate was concentrated yielding 14.5 g (98%) of the desired amide, mp 147–149°. The infrared spectrum of the amide exhibited an NH band at 2.95 and 3.15 and C=O band at 6.00 μ. The amide was used subsequently without further purification.

The amide was converted into 4-trifluoromethyltetrafluorobenzonitrile VI by the procedure described by Marvel and Martin.[4] The desired product VI, mp 31–32° (37%), was obtained and characterized by high resolution mass spectrometry and F^{19} nmr analysis.

Anal. Calcd for C_8F_7N: mol wt, 242.9919. Found: mol wt, 242.9928.

The F^{19} nmr spectrum exhibited a triplet at −20 ppm (J = 22 cps), one-half of an AA′XX′ pattern at +54.5 and a complicated multiplet at 61.4 ppm with relative areas of 3:2:2, respectively.

2,6-Bis(pentafluorophenoxy)-4-trifluoromethyldifluorobenzonitrile VII.—Sodium pentafluorophenolate (340 mg, 1.64 mmol) was added to 4-trifluoromethyltetrafluorobenzonitrile dissolved in 5 ml of DMAC. The reaction, carried out under an atmosphere of nitrogen, was stirred and heated at 50° for 24 hr. The solvent was distilled under vacuum (water aspirator) and the remaining residue (0.55 g) was dissolved in benzene. The benzene solution was placed on an alumina column and eluted with a benzene–petroleum ether (30–60°) solution (1:1). In this manner a yellow oil (0.35 g) was obtained which solidified on standing, mp 78–82°. Recrystallization from hexane afforded 0.25 g (50%) of the product VII, mp 89–91°.

The product VII was characterized by high resolution mass spectrometry and F^{19} nmr and infrared spectral analysis.

Anal. Calcd for $C_{20}F_{15}NO_2$: mol wt, 570.9681; Found: mol wt, 570.9690.

The F^{19} nmr spectrum exhibited typical pentafluorophenoxy absorptions at 79.1, 82.8, and 85.8 (relative area 4:2:4), a triplet at −19.8 (J = 24 cps, relative area 3), and a quartet of quintets at +53.4 ppm (J = 1 cps, relative area 2).

The infrared spectrum of both compound VI and VII exhibited a weak CN band at 4.45 μ.

Registry No.—I, 2263-53-8; II, 15895-67-7; III, 15963-72-1; IV, 16031-36-0; VI, 15895-68-8; VII, 16065-60-4.

(3) C. Tamborski and E. J. Soloski, *J. Org. Chem.*, **31**, 746 (1966).
(4) C. S. Marvel and M. M. Martin, *J. Amer. Chem. Soc.*, **80**, 6603 (1958).

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The Degradation of (−)-4-Methylisopulegone to (+)-2-Isopropyl-2-methylsuccinic Acid[1]

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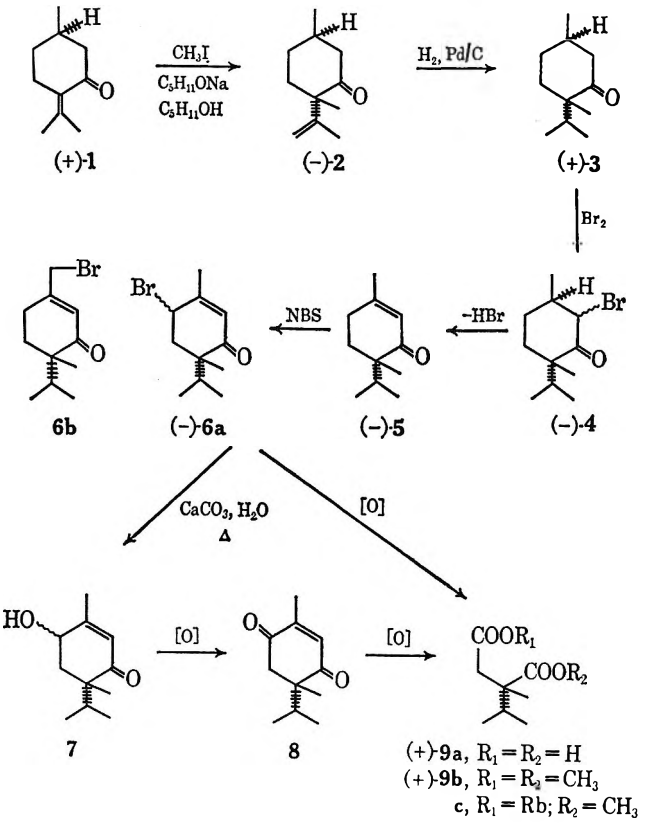
The conversion of (−)-4-methylisopulegone [(−)-4-methyl-*p*-menth-8(9)en-3-one)] (**2**) into (+)-2-isopropyl-2-methylsuccinic acid (**9a**) and the structures of the intermediate products are reported. The absolute configuration of **2** has been unequivocally established by X-ray crystallography of the rubidium salt of the half-methyl ester of (+)-2-isopropyl-2-methylsuccinic acid (**9c**). The acid **9a** is important since it is a degradation product of several terpenes,[3] including (+)-camphor,[4] (+)-thujone,[5] and (+)-sabinene,[6] and has been used to establish the absolute configuration of these and related molecules. We had previously arrived at an incorrect assignment of the absolute configuration of **2** through a quasi-racemate study involving (+)-2-isopropyl-2-methylglutaric acid (**11a**) and (+)-2-isopropylglutaric acid. Since quasi-racemate formation was observed between these acids, we had concluded that the isopropyl groups of these two molecules should have opposite configurations.[7] The paucity of material at that time prevented degradation to 2-isopropyl-2-methylsuccinic acid of known absolute configuration.[8] We have devised and now report a successful degradation of **2** which provides enough **9a** for complete characterization and optical rotation studies.

The reaction sequence used in the degradation is shown in Scheme I, which includes the alkylation of (+)-pulegone (**1**) to (−)-**2**. The latter was isolated and purified as previously reported.[7a] The structure of **2** was confirmed by ir, mass, nmr, and uv spectral data. Catalytic hydrogenation of **2** afforded the expected (+)-4-methyl-*p*-menth-3-one (**3**). Its conversion into the unsaturated ketone **5** *via* the crystalline bromo ketone **4** was also accomplished.[7a]

SCHEME I



All previous attempts at degrading the unsaturated ketone **5** to **9a** failed. We therefore sought a degradation route in which we could activate or substitute C-4 of the unsaturated ketone **5** in such a way that 2-isopropyl-2-methylsuccinic acid could be obtained. Allylic bromination of **5** with N-bromosuccinimide in carbon tetrachloride yielded an unsaturated bromo ketone. This bromination product might be **6a** or **b**. The structure **6a** was apparent from the nmr spectrum, which shows a sharp singlet at τ 8.15 (3 H) due to a vinylic methyl group, whereas the parent ketone **5** shows this methyl signal at 8.10 (3 H). The shift is attributed to the inductive effect exerted by the bromide substituent. The absence of absorption due to allylic methylene protons in the τ 7.5–8.0 region and the survival of the methyl group during bromination provide convincing evidence that structure **6a** is correct. Additional evidence for the formation of a monobromination product is gained from the bromine analysis. Oxidation of **6a** with alkaline potassium permanganage gave **9a**, mp 128–130°, $[\alpha]^{24}D$ +15° (*c* 0.8, C_2H_5OH). A mixture of **9a** obtained from the degradation with an authentic sample of (+)-**9a** showed no depression in melting point.[9] The infrared spectra of these samples were identical, and the mass fragmentation patterns of **9a** and **9b** confirm the structure assignment to **9a**.

(1) (a) This study was initiated before the X-ray crystallography studies were published.[1b] (b) M. R. Cox, H. P. Koch, W. B. Whalley, M. B. Hursthouse, and D. Rogers, *Chem. Commun.*, 212 (1967).

(2) (a) M. V. Kulkarni, Ph.D. Thesis, Oklahoma State University, Stillwater, Okla., May 1967. (b) Address correspondence and reprint requests to this author.

(3) L. Ahlquist, J. Asselineau, C. Asselineau, K. Serck-Hanssen, S. Stallberg-Stenhagen, and E. Stenhagen, *Ark. Kemi*, **14**, 171 (1959).

(4) J. Porath, *ibid.*, **1**, 525 (1950).

(5) H. E. Smith, and A. W. Gordon, *J. Amer. Chem. Soc.*, **84**, 2840 (1962).

(6) T. Norin, *Acta Chem. Scand.*, **16**, 640 (1962).

(7) (a) E. J. Eisenbraun, F. Burian, J. Osiecki, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 3476 (1960); (b) A. Fredga, *Tetrahedron*, **8**, 126 (1960).

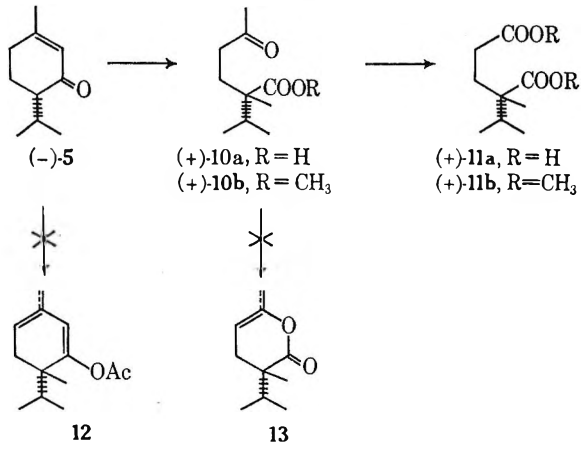
(8) J. Porath, *Ark. Kemi*, **1**, 385 (1949); (b) W. von E. Doering, M. R. Willcott, and M. Jones, *J. Amer. Chem. Soc.*, **84**, 1224 (1962); (c) J. D. Edwards, Jr., and N. Ichikawa, *J. Org. Chem.*, **29**, 503 (1964).

(9) We are grateful to Dr. H. E. Smith for a sample of (+)-**9a**.

The nmr and ir spectra of **9b** support its structure. Comparison of **9b** with the methyl ester of authentic **9a** through gas chromatography on a Carbowax 20M column showed these materials to be homogeneous and indistinguishable. It is assumed that oxidation of **6a** to **9a** proceeds through 4-hydroxy-6-isopropyl-3,6-dimethyl-2-cyclohexen-1-one (**7**), since **7** may be prepared by treating **6a** with a refluxing suspension of aqueous calcium carbonate. The crude product **7** was oxidized with alkaline potassium permanganate and gave, as expected, (+)-2-isopropyl-2-methylsuccinic acid (**9a**).[1b,6]

The degradation route described in Scheme I is deceptively simple but was used only after several other attempts at the degradation of the unsaturated ketone **5** beyond (+)-2-isopropyl-2-methyl-5-oxocaproic acid (**10a**) or **11a** had failed. These attempts included formation of the enol acetate **12** and the enol lactone **13** as shown in Scheme II.

SCHEME II



We believe that these molecules were formed but that reaction conditions necessary for their formation were too severe to permit the products to survive to isolation. The evidence for enol lactone formation was the elimination of water on pyrolysis of **10a** and also the observation of enol lactone carbonyl bands in the infrared spectrum of the pyrolysis product of **10a**. Reaction of the α,β-unsaturated ketone **5** with isopropenyl acetate catalyzed with *p*-toluenesulfonic acid afforded acetone as expected. Gas chromatographic analysis showed eight peaks and, since materials were limited, a pure enol acetate was not obtained. Therefore, these reactions were abandoned in favor of those in Scheme I. During the course of these studies, we repeated the preparation of **10a,b** and **11a,b**, and confirmed the earlier findings regarding the properties of these molecules; in addition, we report nmr and mass spectral data for **10b** and **11b**.

Experimental Section[10]

Isolation and Purification of (+)-Pulegone (1).—Distillation fractions from oil of pennyroyal[11] boiling at 72–75° (0.7 mm) and 75–80° (0.7 mm) were combined and purified by preparative gas chromatography at 180° using a column packed with Chromosorb W coated with LAC-4R-886. Pulegone (**1**) was obtained in 98.7% purity: bp 74–75° (0.7 mm); $\alpha^{24}D$ +23° (neat) [lit.[12] bp 117° (27 mm), $\alpha^{27}D$ +23.6° (neat)]; $\lambda_{max}^{C_2H_5OH}$ 251 mμ (ϵ 7370). Its nmr spectrum in CCl_4 showed absorption at τ 9.0 (3 H, d), 8.7 (1 H, d), 8.0 (6 H, s), 8.1 (4 H, s), and 7.6 (2 H, m).

Preparation of (−)-4-Methylisopulegone (2).—The methylation of 106 g of **1** was carried out as described[12] to give 90 g of crude product. Purification by distillation, preparation of its semicarbazone, recrystallization of the semicarbazone to yield 26 g of material melting at 200–202°, and regeneration by steam distillation in the presence of 52 g oxalic acid yielded 15 g of **2**: bp 89–93° (12 mm); $\alpha^{24}D$ −123° (neat); λ_{max}^{EtOH} 294 mμ (ϵ 51); $\lambda_{max}^{CCl_4}$ 3000, 1720, 1650, 1560, 1470, and 1390 cm^{-1}; nmr (CCl_4), τ 5.05 (2 H, d), 7.3 to 8.2 (6 H, m), 8.3 (3 H, s), 8.7 (1 H, d), 8.9 (3 H, s), and 9.0 (3 H, d). Its mass spectrum showed ion peaks *m/e* 41 (8.2%), 123 (7.7%), 39 (6.0%), 67 (5.4%), 27 (4.4%), and 81 (4.2%) and a parent ion peak *m/e* 166 (2%).

Preparation of (+)-4-Methyl-*p*-menth-3-one (3).—Catalytic hydrogenation of 14 g of **2** as previously described[12] in the presence of 1 g of 10% Pd/C catalyst in 150 ml of 95% ethanol resulted in the uptake of 1 equiv of hydrogen within 45 min. The catalyst was filtered out and the solvent was evaporated and distilled to give 10 g of **3**: bp 85–88° (23 mm); $\alpha^{24}D$ +19° (neat); $\lambda_{max}^{CCl_4}$ 2825, 1710, 1450, and 1375 cm^{-1}; nmr (CCl_4), τ 9.2 (3 H, d), 9.1 (3 H, s), 9.0 (6 H, 2d), 8.4 (1 H, d), 8.2 (1 H, d), 8.0 (2 H, s), and 7.5 to 7.85 (4 H, m). Its mass spectrum showed a molecular ion *m/e* 168 (0.6%), and other prominent, fragments *m/e* 55 (10%), 41 (9.6%), 126 (8.2%), 69 (6.8%), 27 (5.1%), and 43 (4.8%).

Preparation of (−)-2-bromo-6-isopropyl-3,6-dimethylcyclohexanone (4) was carried out as previously described[7a] on 4.6 g of **3** to give 6.2 g of colorless product, bp 140–142° (0.9 mm), which, after recrystallization from *n*-hexane, melted at 79–81°: $[\alpha]^{24}D$ −149° (*c* 1.2; $CHCl_3$); $\lambda_{max}^{CCl_4}$ 1727, 1460, and 1400 cm^{-1}; λ_{max}^{DMSO} 1712 cm^{-1}. There was no shift in the carbonyl-stretching frequency of **3** and **4** when a spectrum taken in DMSO was compared with the corresponding one obtained in CCl_4. The nmr spectrum (in $CDCl_3$) showed bands at τ 9.3 (3 H, s), 9.2 [3 H, 2d (J = 3 cps)], 8.95 [6 H, 2d (J = 5 cps)], 7.6–8.5 (6 H, m), and 4.9 [1 H, d (J = 5 cps)].

Preparation of (−)-6-Isopropyl-3,6-dimethyl-2-cyclohexen-1-one (5).—Dehydrobromination of 1.64 g of **4** as previously described[7a] gave 0.8 g of **5**: $[\alpha]^{24}D$ −81° (*c* 1.4, in $CHCl_3$); λ_{max}^{EtOH} 235 and 320 mμ (log ϵ 4.12 and 1.85); $\lambda_{max}^{CCl_4}$ 2950, 1665, 1550, 1440, and 1380 cm^{-1}; nmr (CCl_4), τ 9.1–9.3 (9 H, s), 8.8 [1 H, d (J = 3.5 cps)], 8.1 (3 H, s), 7.8 (4 H, m), 4.3 (1 H, s). The mass spectrum showed most intense peaks *m/e* 82 (26.5%), 124 (8.7%), 41 (6.9%), 39 (6.3%), 27 (5.0%), and 109 (3.1%), and a molecular ion *m/e* 166 (0.7%).

(−)-4-Bromo-6-isopropyl-3,6-dimethyl-2-cyclohexen-1-one (6a) was prepared by heating N-bromosuccinimide (1.35 g) and 1 g of **5** in 25 ml of CCl_4 for 1 hr under a nitrogen atmosphere. The hot solution was filtered and the solvent was evaporated. Distillation [bath temperature 85° (1.2 mm)] of the residue gave 0.75 g of **6a**: $[\alpha]^{25}D$ −37° (*c* 1.1, $CHCl_3$); λ_{max}^{DMSO} 1650, 1430, and 1380 cm^{-1}. The nmr spectrum ($CHCl_3$) showed bands at τ 9.25–9.05 (9 H, s), 8.75 [1 H, d (J = 3.5 cps)], 8.15 (3 H, s), 7.8 (2 H, d), and 4.35 (2 H, m). *Anal.* Calcd for $C_{11}H_{17}OBr$: Br, 32.65. Found: Br, 32.47.

4-Hydroxy-6-isopropyl-3,6-dimethyl-2-cyclohexen-1-one (7) was prepared by adding the bromo ketone **6a** (0.5 g) to a stirred suspension of 2 g of calcium carbonate[13] in 20 ml of water; the suspension was boiled for 1 hr, cooled, and extracted with ether. The ether extract was dried with magnesium sulfate, filtered, and concentrated. The viscous liquid (0.250 g) was directly

(10) A Beckman GC-2A or an F & M 700 gas chromatography apparatus was used. The columns, heated at 180–190°, were 10 ft × 0.25 in. and were packed with acid-washed Chromosorb W, 60–80 mesh, coated with LAC-4R-886 or Carbowax 20M. Infrared spectra were obtained with a Beckman IR-5A spectrometer; the nmr spectra were determined in CCl_4 on a Varian A-60 spectrometer using tetramethylsilane as the internal standard (τ 10); abbreviations used are d = doublet, m = multiplet, and s = singlet. Melting points were obtained in open tubes with a Thomas-Hoover apparatus, and are not corrected. The mass spectra were determined at 70 eV on a CEC 21-103C mass spectrometer.

(11) Supplied by Fritzsche Bros., New York, N. Y.

(12) C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *J. Amer. Chem. Soc.*, **83**, 4433 (1961).

(13) S. B. Soloway and F. B. LaForge, *J. Amer. Chem. Soc.*, **69**, 979 (1947).

oxidized with alkaline potassium permanganate without purification. Its spectral properties were $\lambda_{max}^{CCl_4}$ 3400, 2950, 1650, and 1050 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 235 mμ (log ε 4.9); nmr (CCl_4), τ 9.1–9.2 (9 H, s), 8.75 (1 H, d), 8.05 (3 H, s), 7.85 (2 H, d), 6.4 (1 H, s), 6.1 (1 H, s), and 4.35 (1 H, s).

Permanganate Oxidation of 6a to 9a.—The bromo ketone **6a** (0.35 g) was added to 3 ml of 6% NaOH and the mixture was cooled to 10° with an ice water bath. To the cooled solution was added 10 ml of 0.17 *M* $KMnO_4$, the suspension was stirred overnight and filtered, and the filtrate was acidified with dilute HCl and then continuously extracted with ether. The ether layer was dried over $MgSO_4$, filtered, and concentrated. The crude solid product was sublimed at 110° (0.8 mm) to give 150 mg of **9a**. Recrystallization from 95% ethanol gave material melting at 128–130°: $[\alpha]^{24}D$ +15° (*c* 0.8, in ethanol); $[\alpha]_{280}$ +358°, $[\alpha]_{260}$ +345°, $[\alpha]_{248}$ +276°, $[\alpha]_{232}$ +131°, $[\alpha]_{225}$ +508° (*c* 0.16, CH_3OH); CD, $[\theta]_{275}$ +6730, $[\theta]_{217}$ +2977, $[\theta]_{200}$ +4140 (*c* 0.16, CH_3OH). The infrared spectrum of **9a** showed bands at λ_{max}^{KBr} 3000, 1758, 1710, 1440, and 1370 cm^{-1}. The melting point of **9a** was not lowered when it was mixed with an authentic sample.[9] The mass spectrum of **9a** showed an intense peak at *m/e* 69 (18.6%), 41 (16.0%), 84 (9.0%), 39 (8.2%), 27 (6.6%), 43 (5.0%), and 114 (1.8%).

The dimethyl ester **9b**, prepared by treating **9a** with diazomethane, was distilled at bath temperature 128° (2.3 mm): $[\alpha]^{24}D$ +30° (*c* 0.83, $CHCl_3$); ORD as a positive plain curve $[\alpha]_{393}$ +24°, $[\alpha]_{345}$ +78°, $[\alpha]_{290}$ +208° (*c* 0.50, CH_3OH); $\lambda_{max}^{CCl_4}$ 2920, 1743, 1550, 1440, 1360, and 1220 cm^{-1}; nmr (CCl_4), τ 8.7–9.2 (9 H, s), 7.9 [1 H, d (J = 3 cps)], 7.45 (2 H, s), and 6.3 (6 H, d). The mass spectrum of **9b** showed prominent peaks at *m/e* 15 (4.4%), 26 (2.7%), 27 (7.5%), 28 (2.6%), 29 (7.6%), 31 (26%), 43 (6.7%), 45 (9.9%), and 46 (4.0%). The molecular ion at *m/e* 202 was not detected.

Permanganate Oxidation of 7.—The oxidation procedure previously described was applied to 150 mg of **7** in 2 ml of 6% NaOH to which was added 5 ml of 0.17 *M* potassium permanganate solution. The reaction gave 70 mg of **9a**, mp 128–130°.

(+)-2-Isopropyl-2-methyl-5-oxocaproic Acid (10a).—The following mass spectral, infrared, and circular dichroism data were obtained for **10a**: *m/e* 43 (9.3%), 55 (8.0%), 27 (6.8%), 83 (6.7%), 41 (6.6%), and 39 (4.5%); $\lambda_{max}^{CCl_4}$ 3050, 1710, 1430, and 1380 cm^{-1}; $[\theta]_{299}$ +231, $[\theta]_{285}$ +297, $[\theta]_{232}$ −264, $[\theta]_{223}$ −99 (*c* 0.31, CH_3OH).

(+)-Methyl 2-Isopropyl-2-methyl-5-oxocaproate (10b).—The following mass spectral, infrared, optical rotatory dispersion, and nmr data were obtained for **10b**: *m/e* 43 (14.1%), 15 (6.0%), 41 (5.9%), 83 (5.7%), and 55 (4.7%); $\lambda_{max}^{CCl_4}$ 2900, 1750, 1720, and 1250 cm^{-1}; $[\alpha]_{400}$ +32°, $[\alpha]_{375}$ +40°, $[\alpha]_{350}$ +56°, $[\alpha]_{325}$ +96°, $[\alpha]_{305}$ +152°, $[\alpha]_{265}$ −134°, and $[\alpha]_{250}$ −28° (*c* 0.60, dioxane); nmr (CCl_4), τ 9.25 (3 H, s), 9.05 (6 H, 2d), 8.30 (1 H, d), 8.20 (2 H, s), 7.95 (3 H, s), 7.80 (2 H, m), and 6.40 (3 H, s).

(+)-2-Isopropyl-2-methylglutaric Acid (11a).—The following mass spectral infrared, and optical rotatory dispersion data were obtained for **11a**: *m/e* 69 (18.6%), 41 (16.0%), 84 (9.0%), 39 (8.2%), 27 (6.5%), and *m/e* 43 (5.0%); λ_{max}^{KBr} 3000, 1758, 1710, 1440, and 1370 cm^{-1}; $[\alpha]_{340}$ +44°, $[\alpha]_{303}$ +56°, $[\alpha]_{245}$ +90° (*c* 0.51, dioxane).

(+)-Dimethyl 2-Isopropyl-2-methylglutarate (11b).—The following mass spectral, infrared, rotatory dispersion, and nmr were obtained for **11b**: *m/e* 43 (14.1%), 15 (6.0%), 41 (5.9%), 83 (5.7%), 55 (4.7%), and 27 (4.0%); $\lambda_{max}^{CCl_4}$ 3000, 1743, 1440, and 1380 cm^{-1}; $[\alpha]_{375}$ +36°, $[\alpha]_{330}$ +52°, and $[\alpha]_{240}$ +144° (*c* 0.8, CH_3OH); nmr (CCl_4), τ 9.1 (3 H, s), 9.0 (6 H, weak s), 7.8–8.4 (5 H, broad m), and 6.4 (6 H, s).

Registry No.—**1**, 15815-63-1; **2**, 5298-65-7; **3**, 15815-65-3; **4**, 15815-66-4; **5**, 15815-67-5; **6a**, 15815-68-6; **7**, 15815-69-7; **9a**, 5033-83-0; **9b**, 15815-71-1; **10a**, 15815-75-5; **10b**, 15815-72-2; **11a**, 15815-73-3; **11b**, 15815-74-4.

Acknowledgments.—We thank Mr. M. C. Hamming, Continental Oil Co., for mass spectra and Dr. O. C. Dermer for having read the manuscript.

Alternate Precursors in Biogenetic-Type Syntheses. III.[1] A Ring D Indoline Analog of the Aporphine Alkaloids. Indole as the Alkylating Agent in the Friedel–Crafts Reaction

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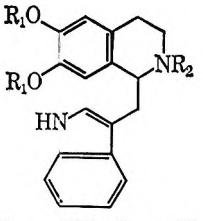
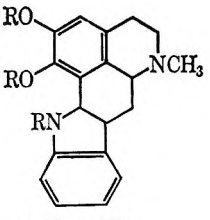
In the first[2] paper of this series we suggested the possible biogenetic conversion of an indole analog of norlaudanosoline into an indole analog of morphine. Since it is well known that norlaudanosoline also can lead to the aporphine alkaloids,[3] the logical development of this theme is the conversion of an indole analog of norlaudanosoline into an indole analog of an aporphine. Chemically, the preferred method of cyclizing the possible biogenetic intermediate **3** seemed to be the alkylation of the benzene ring by the 2,3-double bond of the indole nucleus. Although the alkylation of a benzene ring by an indolenium salt has been described by Harley-Mason and Waterfield,[4] these authors also reported that 1-methyltryptamine and catechol do not react. However, in our case the two reactive centers would be held in a more favorable steric relationship.

The tetrahydroisoquinoline **1** was prepared from N-(3,4-dimethoxyphenethyl)indole-3-acetamide *via* a Bischler–Napieralski cyclization and reduction. Treatment with ethyl formate followed by lithium aluminum hydride reduction converted **1** into its N-methyl derivative (**2**). Strong acid should now bring about hydrolysis of the dimethoxy groups to produce the indole analog of norlandanosoline (**3**) which might



1, R_1 = CH_3; R_2 = H
2, R_1 = CH_3; R_2 = CH_3
3, R_1 = H; R = CH_3



4, R = H
5, R = C(=O)CH_3

well cyclize under the conditions being utilized for hydrolysis. Accordingly, when **2** was refluxed in concentrated hydrobromic acid, the product isolated analyzed for a dihydroxy dihydrobromide indicative of hydrolysis followed by cyclization to **4**, a ring D indoline analog of the aporphine alkaloids. Ultraviolet absorption in acid at 261 mμ (ε 9300), 268 (1300), and 291 (3900) is also consistent[4] with the cyclized compound **4** and not **3**. For further characterization **4** was converted into its triacetyl derivative **5**, whose

(1) For Part II, see G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *J. Org. Chem.*, **32**, 2555 (1967).
(2) G. C. Morrison, R. O. Waite, F. Serafin, and J. Shavel, Jr., *ibid.*, **32**, 2551 (1967).
(3) B. Frank and G. Blasche, *Ann.*, **695**, 144 (1966), and references therein.
(4) J. Harley-Mason and W. R. Waterfield, *Tetrahedron*, **19**, 65 (1963).

nmr spectrum showed the four indoline aromatic protons at 7.2 ppm as a complex pattern and the proton of the diacetoxybenzene at 6.9 ppm as a singlet.

The cyclization of **3** to **4** appears to be the first example of participation of the 2,3-double bond of indole as the alkylating agent in the Friedel–Crafts reaction.

Experimental Section[5]

The melting points were determined using a Thomas–Hoover apparatus which had been calibrated against known standards. The infrared spectra were recorded with a Baird Model 455 instrument in chloroform solutions. The ultraviolet spectra were obtained with a Beckman DKI spectrophotometer in 95% ethanol solutions. The nmr spectra were determined with a Varian Associates A-60 spectrometer in deuterated dimethyl sulfoxide solutions unless otherwise noted.

1,2,3,4-Tetrahydro-1-(indol-3-ylmethyl)-6,7-dimethoxyisoquinoline (1).—A solution of 204 g of N-(3,4-dimethoxyphenethyl)indole-3-acetamide[6] in 450 ml of phosphorus oxychloride was allowed to stand at room temperature for 20 hr. The reaction mixture was poured into 3 l. of ether. The precipitate was rubbed up to a gummy consistency and the supernatant was decanted. The gum was then washed with an additional 1.5 l. of ether. The residue was dissolved in 3 l. of ethanol and diluted with 500 ml of water and the pH was adjusted to 3 with 10% sodium hydroxide solution. Sodium borohydride (50 g) was added portionwise while the temperature was held at 20–30°. After the addition had been completed stirring was continued for an additional 30 min. The pH was adjusted to below 2 with 20% hydrochloric acid and then above 11 with 40% sodium hydroxide solution. After the addition of 1200 ml of water, the mixture was extracted with ether. The ether layer was dried over sodium sulfate and the solvent was removed. Recrystallization of the residue from benzene gave 87 g (45%) of a solid: mp 158–159°; γ_{max} 3440 cm^{-1} (indole NH); λ_{max} mμ (ϵ) 221 (43,400), 282 (10,300), and 290 sh (9250). The nmr spectrum in deuteriochloroform showed the two aromatic protons of the dimethoxybenzene ring at 6.65 (singlet) and 6.85 (singlet) ppm. The five aromatic protons of the indole system formed a complex pattern between 7.0 and 7.8 ppm.

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.50; H, 6.62; N, 8.44.

1,2,3,4-Tetrahydro-1-(indol-3-ylmethyl)-6,7-dimethoxy-2-methylisoquinoline (2).—A solution of 30.0 g of 1,2,3,4-tetrahydro-1-(indol-3-ylmethyl)-6,7-dimethoxyisoquinoline in 300 ml of ethyl formate was refluxed for 25 hr. On standing there was deposited 30 g of a solid which was dissolved in 1 l. of tetrahydrofuran and added to a suspension of 10.0 g of lithium aluminum hydride in 250 ml of tetrahydrofuran. After the addition had been completed stirring was continued for 6 hr. The excess hydride was destroyed by the cautious dropwise addition of water. The reaction mixture was filtered and the solvent was removed. The residue, after recrystallization from benzene–Skellysolve B, gave 25.5 g (67%) of a crystalline solid, mp 125–127°. Further recrystallization gave an analytical sample, mp 126–127°.

Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.88; H, 7.22; N, 8.54.

4,5,6,6a,7,7a,12,12a-Octahydroisoquino-6-methyl[8,8a,1-*a*,*b*]-carbazole-1,2-diol Dihydrobromide Monohydrate (4).—A solution of 10.0 g of 1,2,3,4-tetrahydro-1-(indol-3-ylmethyl)-6,7-dimethoxy-2-methylisoquinoline in 150 ml of hydrobromic acid was refluxed for 15 hr. The reaction mixture was concentrated *in vacuo* (100 mm) to 100 ml. On standing there was deposited 2.8 g (20%) of a crystalline solid, mp 247–257°. Concentration to 30 ml gave an additional 3.5 g (25%), mp 271–277°. Recrystallization from water gave an analytical sample: mp 260–265°; λ_{max} mμ (ϵ) 240 infl (9800) and 291 (5800).

Anal. Calcd for $C_{19}H_{20}N_2O_2 \cdot 2HBr \cdot H_2O$: C, 46.74; H, 4.95; N, 5.74; Br, 32.73. Found: C, 46.92; H, 5.08; N, 5.99; Br, 32.55.

12-Acetyl-4,5,6,6a,7,7a,12,12a-octahydro-6-methylisoquino-[8,8a,1-*a*,*b*]carbazole-1,2-diol Diacetate (5).—To a solution of 10.0 g of 4,5,6,6a,7,7a,12,12a-octahydroisoquino-6-methyl-[8,8a,1-*a*,*b*]carbazole-1,2-diol dihydrobromide monohydrate in 250 ml of pyridine was added 100 ml of acetic anhydride. After standing for 20 hr at room temperature the volatiles were removed *in vacuo* at 50°. Chromatography of the residue on neutral alumina gave an oil on elution with methylene chloride. Crystallization from benzene–Skellysolve B gave 3.0 g (30%) of a solid, mp 182–183.5°. Further recrystallization gave an analytical sample: mp 185–186°; λ_{max} mμ (ϵ) 248 (11,700), 278 (4000), and 288 sh (2800); γ_{max} 1770 (C=O, esters) and 1660 cm^{-1} (C=O, amide).

Anal. Calcd for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45. Found: C, 69.14; H, 6.15; N, 6.57.

Registry No.—1, 15832-21-0; 2, 15832-22-1; 4, 15856-51-6; 5, 15832-23-2.

(5) Melting points are corrected. The authors are indebted to Mr. A. Lewis and his associates, to Mr. R. Puchalski for the spectral data, and to Mrs. U. Zeek for analytical determinations.

(6) G. C. Morrison, R. O. Waite, and J. Shavel, Jr., *J. Heterocycl. Chem.*, **3**, 540 (1966).

Fluoride-Induced Cleavage of the Carbon–Phosphorus Bond in Diethyl Trichloromethylphosphonate. A New Source of Dichlorocarbene and Dialkyl Phosphorofluoridates[1]

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Although the carbon–phosphorus bond in dialkyl trichloromethylphosphonates is cleaved by warming with aqueous alkali,[3] it has been reported that in the absence of alkali this bond is stable. Refluxing with concentrated or aqueous acids,[4] alcohols or phenols[5,6] does not affect the carbon–phosphorus bond. The reaction of these esters with primary amines was at first believed to be a case of carbon–phosphorus bond scission,[7] but this was later disproved.[8]

While attempting to prepare diethyl trifluoromethylphosphonate through halogen exchange by warming diethyl trichloromethylphosphonate (I) with potassium fluoride, it was noted that a significant quantity of chloroform was produced. It was then discovered that the potassium fluoride used was actually the dihydrate.

Although a little surprising, this was interpreted as a carbon–phosphorus bond scission, with the formation of the trichloromethide ion (II) and diethyl phosphoro-

(1) Presented in part at the 153rd National Meeting of the American Chemical Society, Miami, Beach, Fla., April 1967, p O29.

(2) To whom inquiries should be directed.

(3) I. S. Bengelsdorf, *J. Amer. Chem. Soc.*, **77**, 6611 (1955).

(4) I. S. Bengelsdorf and L. B. Barron, *ibid.*, **77**, 2869 (1955).

(5) P. C. Crofts and I. M. Downie, *J. Chem. Soc.*, 2559 (1963).

(6) A. W. Frank, *J. Org. Chem.*, **29**, 3706 (1964).

(7) G. Kamai, *Dokl. Akad. Nauk SSSR*, **55**, 219 (1947); *Chem. Abstr.*, **41**, 5863 (1947).

(8) (a) A. Ya. Yakubovich and V. A. Ginsburg, *ibid.*, **82**, 273 (1952); *Chem. Abstr.*, **47**, 2685 (1953); (b) A. Ya. Yakubovich and V. A. Ginsburg, *Zh. Obshch. Khim.*, **24**, 1465 (1954); *Chem. Abstr.*, **49**, 10834 (1955); (c) K. C. Kennard and C. S. Hamilton, *J. Amer. Chem. Soc.*, **77**, 1156 (1955); (d) T.-S. Tung and S.-T. Chern, *Hua Hsueh Hsueh Pao*, **24**, 30 (1958); *Chem. Abstr.*, **53**, 3113, 2114 (1959).

$$\underset{\text{I}}{CCl_3P(O)(OEt)_2} + KF \longrightarrow K^+ + \underset{\text{II}}{[CCl_3]^-} + \underset{\text{III}}{FP(O)(OEt)_2} \quad (1)$$

fluoridate (III) (see eq 1). In the presence of the water of hydration, the trichloromethide ion (II) would immediately be hydrolyzed to chloroform[9] (eq 2),

$$\underset{\text{II}}{[CCl_3]^-} + H_2O \longrightarrow OH^- + CHCl_3 \quad (2)$$

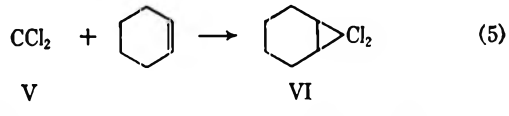
and the diethyl phosphorofluoridate (III) would be hydrolyzed with the formation of diethyl hydrogen phosphate (IV)[10] (eq 3).

$$\underset{\text{III}}{FP(O)(OEt)_2} + H_2O \longrightarrow \underset{\text{IV}}{HOP(O)(OEt)_2} + HF \quad (3)$$

The procedure was repeated using anhydrous potassium fluoride. Upon warming diethyl trichloromethylphosphonate with anhydrous potassium fluoride a good yield of diethyl phosphorofluoridate (III) was obtained. Apparently, under mild conditions, and in the absence of water, carbon–phosphorus bond scission had again occurred. It was not clear what the other product(s) of the reaction might be because, from the stoichiometry of the reaction, the other products are the potassium ion and the trichloromethide ion (II).

It has been shown that dichlorocarbene (V) is produced from the trichloromethide ion in several other reactions by the loss of chloride ion[11] (eq 4). Dichlorocarbene (V) adds readily to olefins to form cyclopropane derivatives;[11] so the reaction was repeated in the presence of cyclohexene and 7,7-dichlorobicyclo-[4.1.0]heptane (dichloronorcarane) (VI) was isolated in 40% yield (eq 5).

$$\underset{\text{II}}{[CCl_3]^-} \longrightarrow Cl^- + \underset{\text{V}}{CCl_2} \quad (4)$$



V VI (5)

Anhydrous sodium fluoride is almost completely ineffective in promoting the cleavage. Lithium fluoride and calcium fluoride are completely ineffective. Ammonium fluoride works as well, if not better, than potassium fluoride in effecting the scission. Antimony trifluoride apparently is somewhat active and silver monofluoride produces a rather exothermic reaction with diethyl trichloromethylphosphonate resulting in carbon–phosphorus bond scission. The carbon–phosphorus bonds in diethyl dichloromethylphosphonate, diethyl chloromethylphosphonate, and diethyl methylphosphonate are unaffected by warming with anhydrous potassium fluoride.

If methanol is used as a solvent to increase the solubility of the potassium fluoride in diethyl trichloromethylphosphonate (I) the reaction proceeds quite exothermically at room temperature to give diethyl methyl phosphate (VII) (eq 6).

$$\underset{\text{I}}{CCl_3P(O)(OEt)_2} + KF + MeOH \longrightarrow \underset{\text{VII}}{MeOP(O)(OEt)_2} \quad (6)$$

The mechanism and synthetic applications of this cleavage are presently under investigation.

(9) J. Hine and A. M. Dowell, Jr., *J. Amer. Chem. Soc.*, **76**, 2688 (1954).
(10) N. B. Chapman and B. C. Saunders, *J. Chem. Soc.*, 1010 (1948).
(11) W. von E. Doering and A. K. Hoffman, *J. Amer. Chem. Soc.*, **76**, 6162 (1954).

Experimental Section

Reaction with Potassium Fluoride Dihydrate.—After heating a mixture of 51.1 g (0.2 mol) of diethyl trichloromethylphosphonate and 46.4 g (0.49 mol) of potassium fluoride dihydrate at reflux (71°) for 30 min, 20 g (84%) of chloroform (bp 58–60 (740 mm), $n^{25}D$ 1.4437) was distilled from the reaction mixture.

Reaction with Anhydrous Potassium Fluoride.—In a flask fitted with a reflux condenser protected by a calcium chloride tube 206 g (0.81 mol) of diethyl trichloromethylphosphonate and 188 g (3.24 mol) of anhydrous potassium fluoride were stirred over a steam bath for 60 hr. Distillation from the reaction flask gave 108.5 g (86%) of diethyl phosphorofluoridate: bp 80–80.5 (32 mm); $n^{27}D$ 1.3710; d^{27}_4 1.1399.

Anal. Calcd for $C_4H_{10}FO_3P$: C, 30.78; H, 6.46; F, 12.17; P, 19.85. Found: C, 30.78, 30.83; H, 6.23, 6.24; F, 12.15, 12.20; P, 19.97, 19.81.

Note: Phosphorofluoridates are known to be extremely toxic. At lower concentration their vapors have a myotic effect (pupil constriction) on the eye and at higher concentrations they can cause respiratory collapse.[12]

Reaction in Cyclohexene.—In a flask fitted with a reflux condenser protected by a calcium chloride tube 112 g (0.5 mol) of diethyl trichloromethylphosphonate, 58 g (1.0 mol) of anhydrous potassium fluoride, and 82 g (0.5 mol) of cyclohexene were stirred while heated in an oil bath at 110° for 24 hr. After filtering, the precipitate was washed with two 50-ml portions of dry ether. The filtrate and washings were combined and the ether and unreacted cyclohexene were distilled out. The residue was stirred with 100 ml of water for 4 hr at 60°. The hydrolysate was extracted with two 50-ml portions of petroleum ether. After drying over magnesium sulfate the petroleum ether was removed from the combined extracts at 20 mm on a rotary evaporator. Distillation of the residue gave 33.0 g (40.0%) of dichloronorcarane, bp 84–85° (17 mm), $n^{24}D$ 1.5010.

Anal. Calcd for $C_7H_{10}Cl_2$: C, 50.93; H. 6.11; Cl, 42.96. Found: C, 50.83, 50.93; H, 6.11, 6.04; Cl, 43.01, 42.90.

Reaction in Methanol.—Diethyl trichloromethylphosphonate (25.6 g, 0.1 mol) was added, dropwise at first, to 11.6 g (0.2 mol) of anhydrous potassium fluoride, with stirring. When there was no apparent evidence of reaction the remainder of the ester was run into the flask. In about 2 min the temperature began to rise so rapidly that the flask had to be cooled with an ice bath to keep the methanol from refluxing at a rate that exceeded the capacity of the condenser. When the reaction had subsided heat was applied to keep the methanol refluxing for 24 hr. After cooling, 50 ml of ether was added, the solids were filtered, and distillation of the filtrate gave 13.5 g (80%) of diethyl methyl phosphate, bp 104–105° (21 mm), $n^{21}D$ 1.4031.

Registry No.—I, 866-23-9; III, 358-74-7; V, 1605-72-7; VI, 823-69-8; VII, 867-17-4.

(12) B. C. Saunders, "Some Aspects of the Chemistry of Organic Compounds Containing Phosphorus and Fluorine," Cambridge University Press, London, 1957, p 1.

3,5-Dichlorotyrosines. Preparation of D and L Forms[1]

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A number of references to 3,5-dichloro-L-tyrosine have been reported[2–4] which are based on a synthesis

(1) Supported by U. S. Public Health Service Grants CA06519 and AM09429.
(2) F. K. Beilstein, "Handbuch der organische Chemie," Vol. 14, 2nd ed, Part I, Springer-Verlag, Berlin, 1951, p 670; Part II, pp 377, 382.
(3) S. Bouchilloux, *Bull. Soc. Chim. Biol.*, **37**, 255 (1955).
(4) Houben-Weyl's, "Methoden der organischen Chemie," Vol. 5, Part 3, Georg Thieme Verlag, Stuttgart, Germany, 1962, p 685.

described by Zeynek.[5] The product obtained had been variously described as gray, yellow, or brown and as the mono- and dihydrate. A reexamination of the procedure was undertaken and we found that the products formed by this method varied in both composition and color.

A reproducible synthetic method for 3,5-dichlorotyrosine has been developed. Significant was the ease of preparation, coupled with consistent formation of a white solid of definite composition. The compound formed only as the monohydrate and when prepared from L-tyrosine was dextrorotary.

Experimental Section

A 200-ml, three-necked, standard-taper flask was fitted with a glass thermometer, a motor-driven glass stirrer in a Teflon-sealed, gas-tight stopper in the center neck, and a "T" glass standard-taper connection in the remaining neck. One of the "T" openings connected to a chlorine gas supply tank was fitted with a pressure regulator. The remaining "T" opening was connected to a "U" type manometer containing light mineral oil.

A bath containing salt–ice–water was agitated by a magnetic stirrer, and completely surrounded the reaction flask up to the center neck. A 5-g sample of L-tyrosine powder (J. T. Baker Chemical Co.) and 125 ml of propionic acid were well mixed in the flask to obtain a fine dispersion. Both the bath fluid and the reaction mixture were stirred continuously throughout the run.

The bath temperature was dropped to −10°. Chlorine was added to flush out air in the system; this was done by raising the thermometer slightly, thus creating an exit vent, for 30 sec. The thermometer was replaced in position to again make a gas-tight system, and the chlorine regulated to give a manometer reading of about 1 cm of mineral oil. In a period of 18 min, the flask temperature rose to +1°. At this point the bath mixture was adjusted to obtain a flask temperature of 0–5° for a period of 2 hr. After about 8 min from the beginning of chlorination, the flask contents almost cleared to a single phase; only a few crystals remained. Soon thereafter crystals appeared in quantity and the mass thickened, but remained sufficiently fluid for agitation. After about 10 min from the beginning of chlorination, the manometer pressure gradually increased as the chlorine absorption rate diminished. About 3 min later, the chlorine pressure reached a maximum or constant value. The chlorine pressure in the system was kept at a positive value at all times to eliminate the possibility of air or moisture entry through leakage.

Following the 2-hr chlorination period, the "T" connection was quickly removed and replaced with a single-stem standard taper reducer. This was coupled to a large, dry glass trap in series with a water aspirator. Agitation was continued while the system was under vacuum (30 mm). When the volatiles and free chlorine were being removed, the temperature dropped and then rose again to 5°.

After agitation for one more hour at 5°, the dispersion became white in color. The flask contents were then filtered by suction, using a fritted glass, Buchner-type, jacketed, filter funnel through which ice water circulated. The residue was pressed dry to remove additional mother liquor. Filtration was continued until no more solvent was removed. The residue was washed with two 5-ml portions of propionic acid at 0° and again suction was applied until no more filtrate appeared. The filter cake weighed 12.4 g and contained an appreciable amount of mother liquor and propionic acid.

A. Salting-Out Process.—One-half of this crude residue (6.2 g) was dissolved in 62 ml of water at 15° and the small amount of insoluble material was filtered off. To the filtrate, with agitation, was added 13 ml of an aqueous solution containing 3.3 g of sodium acetate trihydrate. After stirring for 10 min, the mixture was refrigerated to 10°, and filtered through a cold fritted glass funnel. The residue was washed three times by dispersing well each time in an equal volume of water at 0°. The residue was sucked dry for 2 hr or more at room temperature to constant weight. The pure product obtained weighed 2.5 g (67.6% yield). *Anal.* Calcd for $C_9H_9NCl_2O_3 \cdot H_2O$: C, 40.30; H, 4.10; N, 5.23; Cl, 26.40. Found: C, 40.35; H, 4.16; N, 5.27; Cl, 26.34.

(5) R. Zeynek, *Z. Physiol. Chem.*, **114**, 275 (1921).

B. Neutralization Process.—The remaining half of the crude residue (6.2 g) was dissolved in 25 ml of water at 15° and filtered. The filtrate was diluted with 200 ml of water, and then kept at 5° during subsequent operations. The solution was neutralized to pH 8 with 1 *N* NaOH with good agitation and again filtered, and the filtrate was brought to pH 3 with 1 *N* hydrochloric acid. Following filtration, the residue was washed by dispersal three times in equal volumes of water and sucked dry. Suction was continued at ambient temperature to constant weight. A white product (2.3 g) was obtained (62.3% yield). *Anal.* Found: C, 40.32; H, 4.13; N, 5.21; Cl, 26.39.

Of the two general processes, the salting-out procedure with sodium acetate solution gave slightly higher yields.

The product had a melting point of 225–228° with decomposition (Nalge microscope-type, polarized melting point apparatus). Ascending chromatography on Whatman No. 1 paper revealed a single ninhydrin-reacting spot at R_f 0.59 in 4:1:1 (v/v/v) 1-butanol–acetic acid–water and at R_f 0.70 in 130:33:40 (v/v/v) 2-propanol–concentrated HCl–water. There was an ultraviolet absorbance peak at 305 mμ. A sample of 3,5-dichlorotyrosine monohydrate allowed to stand under high vacuum at normal temperature in the presence of concentrated H_2SO_4 for 33 days showed weight loss corresponding to 1 H_2O (calcd: 6.7%; found: 6.6%). The compound synthesized from L-tyrosine was dextrorotary, $[\alpha]^{25}D$ +1.16 (*c* 5, 1 *N* HCl), whereas that synthesized from D-tyrosine was levorotary $[\alpha]^{25}D$ −1.13. To confirm the purity of the optical isomers, an enzyme system was used.[6] The large change in optical density at 332 mμ in borate buffer, in the presence of L-amino acid oxidase (*Crotalus adamanteus* venom) and catalase, with the 3,5-dichlorotyrosine prepared from L-tyrosine, was indicative of the L form. The compound synthesized from D-tyrosine, under identical test conditions, was not reactive.

In place of the propionic acid, glacial acetic acid has also been used as an alternative solvent at 20° maximum temperature (care must be taken to prevent solidification of the reaction mixture by keeping the temperature above 16°). The yield and purity of compounds formed using both solvents were identical. The keys to a successful preparation are rigid temperature control and the thorough removal of excess chlorine following halogenation.

Registry No.—3,5-Dichloro-D-tyrosine, 15924-16-0; 3,5-dichloro-L-tyrosine, 15106-62-4.

Acknowledgment.—The authors are grateful to Dr. George Delpierre for the polarimetry measurements.

(6) R. P. Spencer and D. Brock, *Endocrinology*, **70**, 750 (1962).

On the Reaction of 1-Phenylcyclopentanecarbonitrile with Methylmagnesium Iodide. Formation of Bis(1-phenylcyclopentyl) Ketone[1]

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Some years ago, in connection with another problem, we had occasion to prepare 1-phenylcyclopentyl methyl ketone (**1**). We chose the method of Smith and

1

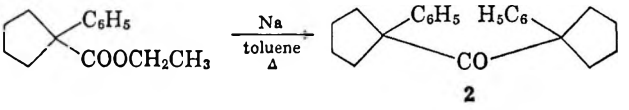
(1) This reaction was first noticed during the doctoral research of Herbert Philip, and is described in his Dissertation, pp 108–109, Loyola University (1959). No structural assignment was made at that time.

coworkers[2] wherein 1-phenylcyclopentanecarbonitrile was treated with methylmagnesium iodide in ether. The initial ketimine was hydrolyzed by these workers to obtain **1** in 57% yield. Their liquid product and its 2,4-dinitrophenylhydrazone and semicarbazone derivatives were characterized by elemental analysis. Recently, MacKenzie, *et al.*,[3] made **1** "in good yield" by the same process. Their material and its semicarbazone were apparently the same as Smith's.

However, in our hands at that time, this reaction took another course. We found that when less ether was used than that employed by Smith and coworkers,[4] a white solid **2**, mp 98.5–99.5°, was observed as the major product of the reaction after acidic work-up. Lesser quantities of recovered nitrile and **1** were also obtained, although our samples of the two aforementioned derivatives of **1** melted far from the reported values.

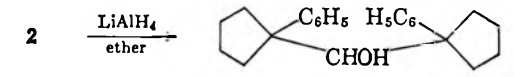
Recently we decided to unravel the apparent mystery involved in this process. First, to check the structure of **1**, its infrared and nmr spectra were determined and found to be consonant with the proposed structure. Furthermore, hypobromite oxidation of **1** led to 1-phenylcyclopentanecarboxylic acid. So the structure of **1** does seem secure. Just why the derivatives we made melted at different temperatures than those reported[2,3] is not known. 2,4-Dinitrophenylhydrazones in particular, however, often exhibit polymorphism, as well as *cis*, *trans* stereoisomerism, and we suggest such may be the situation here. Second, the effect of the concentration of reactants was checked. Under concentrated reactant conditions, **2** was formed in 42% yield while the yield of **1** was only 19%. When the more dilute reactant concentrations employed by Smith were used, however, the yield of white solid **2** fell to 4.1% while that of **1** rose to 32.3%, with 38.2% of unchanged starting nitrile being recovered. Whereas we were unable to duplicate Smith's work any better, it was at least apparent that the solid **2** could have been missed under his conditions. We then turned to the structure of the white solid **2**.

This crystalline solid was nitrogen-free and had a composition by combustion analysis best fitted to $C_{23}H_{26}O$. The oxygen was apparently carbonyl in character from a very sharp and strong absorption at 5.98 μ. The nmr spectrum was simple, with aromatic hydrogens as a sharp multiplet centered at δ 7.18 (5 H's) and two upfield multiplets, one at 2.5–1.53 (4 H's) and another at 1.53–0.92 (4 H's) relative to internal tetramethylsilane (TMS). These facts and others (see Experimental Section), plus the possible aberrations involved in the reaction of Grignard reagents with nitriles, led us eventually to formulate **2** as **bis(1-phenylcyclopentyl) ketone**. A search showed that this compound had actually been prepared in 1952 by van Heyningen[5] in an attempted acyloin condensation of ethyl 1-phenylcyclopentanecarboxylate. The ketone was reported to melt at 93–95° and to have infrared absorptions at 5.94, 9.26, and 9.67 μ. Our reaction product **2** did melt at this temperature, though purified samples melted at 98.5–99.5°, and the infrared spectral agreement was good.



2

As might be expected from its hindered nature, **2** did not form derivatives easily. It was, however, readily reduced to the carbinol **3** with lithium aluminum hydride. Attempted cleavage of **2** either by means of



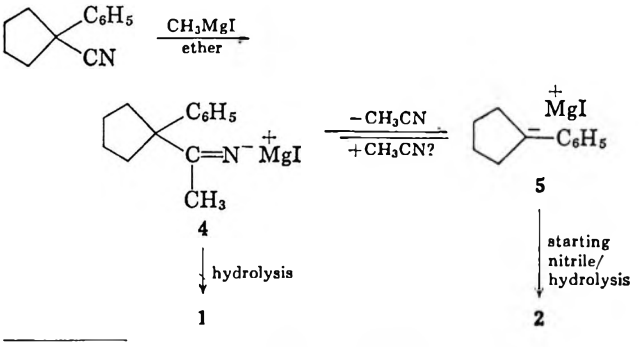
3

sodamide in refluxing toluene or by the recently described[6] use of potassium *t*-butoxide in dimethyl sulfoxide failed. The ketone was recovered unchanged in each case.

The probable initial step in the formation of **2** in this reaction represents an interesting example of what has been termed the "reductive displacement" of nitriles by Grignard reagents.[7] The intermediate imino anion **4**, undoubtedly involved in the "normal" process, can dissociate to some degree to the 1-phenylcyclopentyl anion **5**[8] with loss of acetonitrile. Reaction of **5** with the starting nitrile in the usual way would then produce **2** *via* its imine salt (the free imine was detected in the reaction, see Experimental Section). Eventual hydrolysis of undissociated **4** *via* its imine could lead to **1**, the expected product. It is possible that **1** might also result from **5** and the acetonitrile liberated from **4**. This is improbable, however, because acetonitrile is well known to behave poorly in ketone syntheses of this type because of its acidic α hydrogens.[9]

The postulated exchange of nitrile and magnesio functions in Scheme I has actually been observed on occasion, particularly with polyarylacetonitriles.[10] For instance, propionitrile has been detected in the reaction of diphenylacetonitrile and ethylmagnesium

SCHEME I



(2) P. A. S. Smith, D. R. Baer, and S. N. Ege, *J. Amer. Chem. Soc.*, **76**, 4564 (1954).

(3) S. MacKenzie, S. F. Marsocci, and H. C. Lampe, *J. Org. Chem.*, **30**, 3328 (1965).

(4) Each method used *ca.* threefold excess Grignard reagent. MacKenzie and coworkers[3] also employed threefold excess Grignard, but no other information was given.

(5) E. van Heyningen, *J. Amer. Chem. Soc.*, **74**, 4861 (1952).

(6) P. G. Gassman and F. V. Zalar, *Tetrahedron Lett.*, 3031 (1964).

(7) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p 779.

(8) That this carbanion is relatively easily formed may be surmised from the moderately good (50%) yield of 1-phenylcyclopentanecarboxylic acid obtained upon carbonation of the solution resulting from treatment of 1-phenylcyclopentyl methyl ether with sodium–potassium alloy: G. W. Wheland and R. D. Kleene, *J. Amer. Chem. Soc.*, **63**, 3321 (1941).

(9) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1965, p 214.

(10) Reference 7, pp 779–782.

bromide.[11] Triphenylacetonitrile is another well-documented instance, its reaction with benzylmagnesium chloride affording a 70% yield of triphenylmethane.[12] In this latter case, as opposed to the present one, the intermediate trityl anion apparently was too stable to attack the reactant nitrile, so hydrolysis gave hydrocarbon instead of carbonyl product. Even with these literature precedents, the present illustration of this exchange is nonetheless interesting because it is the first monoarylacetonitrile to behave in this manner.

The effect of reactant concentration is also rationalized by the reaction scheme above. Provided that conversion of starting nitrile into **4** is not overly rapid,[13] the subsequent formation of **2** (as its imine salt) would be faster in more concentrated solutions because the possibility of reaction between **5** and the starting nitrile is increased. As more dilute solutions are employed, the formation of the imine salt of **2** would correspondingly decrease while the conversion of the starting nitrile into **4** would correspondingly increase. With the route to **2** thus impeded, the process would then take the expected path to **1**, as found.

Finally, the rates of the various processes in this reaction must be rather critically balanced, as attempts to find this exchange reaction in homologs of 1-phenylcyclopentanecarbonitrile uniformly failed.[14] Only the expected methyl ketones were observed as products here.

Experimental Section

Melting points and boiling points are uncorrected for stem exposure. The former were determined on a calibrated Fisher-Johns block. The latter were taken during short-path distillations under nonequilibrium conditions and may reflect superheating. Infrared spectra were obtained on Perkin-Elmer Model 21 and Beckman IR-5A instruments and are given in microns (μ). Nmr spectra were determined on a Varian A-60A spectrometer with internal TMS as a standard. Gas–liquid partition chromatography (glpc) was performed on an Aerograph A-90P chromatograph using helium as the carrier gas. Microanalyses were done by Micro-Tech Laboratories, Inc., Skokie, Ill.

Reaction of 1-Phenylcyclopentanecarbonitrile and Methyl Grignard Reagent (Concentrated Reactant Conditions).—1-Phenylcyclopentanecarbonitrile [5.0 g, 29 mmol, freshly prepared from phenylacetonitrile and 1,4-dibromobutane using sodamide;[15] bp 106.5° (0.3 mm); λ^{neat} 4.51 (CN); δ^{neat}_{TMS} 7.6–7.13 m (Ar–H), 2.5–1.5 m (cyclopentyl H's); homogeneous in glpc] in dry ether (6.4 ml) was added over a 5-min period to the Grignard reagent prepared from methyl iodide (12.32 g, 5.54 ml, 88 mmol), magnesium turnings[16] (2.14 g, 88 mg-atoms), and ether (39 ml). The material was then stirred and refluxed 18 hr protected from moisture. To the mixture, cooled to 0°, water (10 ml) was now added dropwise. After this decomposition of the excess Grignard reagent, the total contents were added with vigorous stirring to ice (100 g) and hydrochloric acid (concentrated, 15 ml). The material formed two phases with an interphase of a crystalline substance. The ether phase was separated and processed separately (see below). The aqueous phase, collected together with the solid interphase, was refluxed a further 18 hr, whereupon the crystals were replaced with oil globules. The cooled mixture was then extracted with benzene (thrice with 50 ml). The benzene extracts were combined, washed with aqueous sodium carbonate (10%) and then water to neutrality, dried, and stripped free of benzene. The oily residue partially crystallized on standing. The crystals (**2**) were separated from the oil and washed with cold ethanol. Further crystals were obtained by concentrating these ethanol washings.

In this way there was obtained **2**, identified as **bis(1-phenylcyclopentyl) ketone**, as glistening needles (1.94 g, 42%, mp 94–95°). Purification by recrystallization from ethanol proceeded easily and with little loss and gave **2** as snow-white needles (1.85 g, 40%): mp 98.5–99.5°; λ^{KBr} 5.98 (sharp, >C=O), 3.31, 3.42, 3.52, 6.28, 6.71, 6.92, 7.7 (broad), 8.2 8.85, 9.30, 9.46, 9.70, 10.49, 10.72, 10.93, 11.28, 13.2 (broad), 13.91, 14.33; $\delta^{CCl_4}_{TMS}$ 7.18 (sharp multiplet, Ar–H), 2.5–1.53 m (four cyclopentyl H's per ring), 1.53–0.92 m (other four cyclopentyl H's per ring) (lit.[5] mp 93–95°; λ (medium not stated) 5.94, 9.26, 9.67).

Anal. Calcd for $C_{23}H_{26}O$: C, 86.74; H, 8.23. Found: C, 86.72, 86.97; H, 8.01, 8.21.

The oily portion of the residue was distilled to afford 1.04 g (19%) of **1-phenylcyclopentyl methyl ketone** (**1**): bp 115–120° (3.0 mm); $n^{25}D$ 1.5330; λ^{neat} 5.89 and 7.4 (–$COCH_3$), 3.3, 3.4, 3.5, 6.27, 6.71, 6.92, 6.98, 8.19, 8.5, 8.69, 8.93, 9.31, 9.68, 9.98, 10.36, 10.57, 10.8, 11.0, 13.2, 14.3; δ^{neat}_{TMS} 7.32 m (sharp, Ar–H), 2.80–1.40 m (cyclopentyl H's), 1.85 s (–$COCH_3$); homogeneous by glpc (lit.[2] bp 142–148° (18 mm), 110° (3 mm); $n^{25}D$ 1.5398).

The **2,4-dinitrophenylhydrazone** of **1** was a yellow, microcrystalline solid, mp 107.5–108° from ethanol (lit.[2] mp 145.6–146.2°).

Anal. Calcd for $C_{19}H_{20}O_4N_4$: N, 15.21. Found: N, 15.45.

The **semicarbazone** of **1** was also prepared (white microcrystalline solid from aqueous alcohol, mp 211–215° dec (lit. mp 228.5–231° dec,[2] 228–230°[3]).

Anal. Calcd for $C_{14}H_{19}ON_3$: N, 17.13. Found: N, 17.55.

The ether phase from the reaction was freed of solvent and yielded an oil and a small amount of a semisolid. The latter, while not **2** because of differing spectra, nevertheless did afford **2** upon repeated recrystallization from aqueous alcohol. It was probably ketimine salt that escaped hydrolysis (or perhaps the free imine). The oil (1.21 g, bp 105° (0.5 mm, $n^{20}D$ 1.5324) was shown to be recovered starting nitrile (24.3% recovery) by spectral comparison with starting material.

Hypobromite Cleavage of 1.—Because of the discrepancies between the earlier[2,3] and present samples of **1** and its derivatives, the ketone (0.5 g) was cleaved with excess bromine and sodium hydroxide (2 hr on the steam bath). Bromoform was formed as a heavy oil which was separated. The aqueous phase was well chilled and acidified with hydrochloric acid (using sodium bisulfite to remove the excess bromine liberated). The crystalline white solid (0.2 g, 40%) that precipitated was **1-phenylcyclopentanecarboxylic acid** which had a melting point and mixture melting point with an authentic sample of 156.5–158° and identical infrared spectra (lit.[17] mp 158–159°).

Grignard Reaction under Dilute Reactant Conditions.—The reaction of 1-phenylcyclopentanecarbonitrile (2.57 g, 15 mmol) in dry ether (30 ml) with the Grignard reagent prepared from methyl iodide (6.4 g, 45 mmol), and magnesium turnings[16] (1.09 g, 45 mg-atoms) in ether (30 ml) was performed exactly as described above. From the ether phase after processing the reaction there was isolated starting nitrile (0.98 g, 38.2% recovery, bp 110–111° (0.2 mm)), identified by its infrared spectrum, contaminated slightly with ketone **1**. From the aqueous phase there was obtained ketone **1** containing a trace of starting nitrile (0.91 g, 32.3%, bp 111–112° (0.2 mm)), again identified spectrally, as well as crystalline **2** (0.10 g, 4.1%), also identified by spectral comparison with the material obtained under more concentrated conditions.

Attempted Reactions on 2.—This ketone was relatively inert. It could be recovered essentially quantitatively after treatment with hot sodium hydroxide in aqueous dioxane, bromine in methanol, hot hydrochloric acid, hot 30% sulfuric acid, cold concentrated sulfuric acid, and sodamide in refluxing toluene. Attempted cleavage of the ketone (4.6 mmol) under nitrogen with fresh potassium *t*-butoxide (35 mmol) in purified dimethyl sulfoxide (11 ml) containing water (10 mmol), a recent technique[8] of reputed value in ketone cleavage, gave over 90% recovery of

(11) F. F. Blicke and E. P. Tsao, *J. Amer. Chem. Soc.*, **75**, 5587 (1953).

(12) P. Ramart-Lucas and F. Salmon-Legagneur, *Bull. Soc. Chim. Fr.*, **43**, 321 (1928).

(13) This is a reasonable proviso in that significant nitrile is recoverable from the reaction.

(14) As a rationalization of this point, it might be pointed out that neither the 1-phenylcyclohexyl carbanion nor the 1-phenylcyclobutyl carbanion readily resulted from the same type cleavage (Na–K alloy) of the corresponding methyl ether that easily formed the 1-phenylcyclopentyl analog. *Cf.* ref 8 and J. W. Wilt, L. L. Maravetz, and J. F. Zawadzki, *J. Org. Chem.*, **31**, 3018 (1966).

(15) A. W. Weston, *J. Amer. Chem. Soc.*, **68**, 2345 (1946).

(16) Baker and Adamson Division, Allied Chemical Corp., Code 1904. This magnesium was used throughout the study on all the nitriles.

(17) F. Case, *ibid.*, **56**, 715 (1934).

2.[18] No carbonyl derivatives of 2 could be formed, although attempts in this direction were not exhaustive. All these facts were of assistance in ascribing the structure given to 2.

Reduction of 2 to Bis(1-phenylcyclopentyl)carbinol (3).—Treatment of 2 with excess lithium aluminum hydride in ether at room temperature in the usual manner led to alcohol 3 in 85% yield: mp 97–98° from aqueous ethanol, mixture melting point with 2 depressed (69–88°); λ^{KBr} 2.92 (O–H), 9.68 and 9.81 (C–O), 3.31, 3.36, 3.45, 3.55, 6.29, 6.72, 7.27, 7.41, 7.60, 7.8–8.1 (broad), 8.32, 9.05, 9.30, 10.0, 10.38, 10.6, 11.3, 13.14, 14.40; $\delta_{TMS}^{CCl_4}$ 7.25 m (sharp, Ar–H), 4.07 s (broad, >CHOH), 1.99 s (broad, lost in D_2O, –OH), 1.83–1.0 m (all cyclopentyl H's).

Anal. Calcd for $C_{23}H_{28}O$: C, 86.20; H, 8.81. Found: C, 85.89; H, 8.80.

Reactions of Other 1-Phenylcycloalkanecarbonitriles with Methyl Grignard Reagent.—The cyclopropyl, cyclobutyl, and cyclohexyl analogs were available from earlier work.[19] Small scale (*ca.* 10 mmol) reaction of these with methylmagnesium iodide in ether under the concentrated reactant conditions described earlier for the cyclopentyl case failed to give products analogous to 2 in workable amounts, although traces of unidentified semisolid or solid material was occasionally obtained. The ketone products were collected by glpc or Hickman still distillation, so boiling points were not determined. The cyclohexyl analog gave **1-phenylcyclohexyl methyl ketone** in 26.5% yield, mp 31–33°, lit.[20] mp 33–35° (λ^{melt} 5.88, 7.40 (–$COCH_3$)), and much recovered nitrile.[21] The cyclobutyl member afforded **1-phenylcyclobutyl methyl ketone** in 31.4% yield (oil, λ^{neat} 5.90, 7.40, (–$COCH_3$), lit.[3] bp 56–57° (0.2 mm)) with some starting nitrile again being recovered. Finally, the cyclopropyl example yielded **1-phenylcyclopropyl methyl ketone** in 29.5% yield (oil, λ^{neat} 5.93, 7.40 (–$COCH_3$), 7.80, 8.70, 9.12, 9.72, 13.17, 14.25; lit.[22] bp 122° (25 mm), lit.[23] λ^{neat} *inter alia* 5.86, 7.79, 8.70, 9.12, 9.72, 13.16, 14.24) and, as usual, some starting nitrile. In this case an unidentified oil was isolated from the aqueous phase. Its properties were much unlike those of 2, however, and its spectra suggested that it was a ring-opened derivative of the methyl ketone.

Registry No.—1-Phenylcyclopentanecarbonitrile, 77-57-6; methylmagnesium iodide, 917-64-6; **1**, 4046-09-7; **1** 2,4-dinitrophenylhydrazone, 15811-00-4; **1** semicarbazone, 15811-01-5; **2**, 15811-02-6; **3**, 15811-03-7.

(18) Whereas excellent in some less-hindered cases, this method, as reported,[6] gave only a 9% cleavage of the hindered ketone, camphenilone.

(19) J. W. Wilt and H. Philip, *J. Org. Chem.*, **24**, 616 (1959); J. W. Wilt and D. D. Roberts, *ibid.*, **27**, 3434 (1962).

(20) G. G. Lyle, R. A. Covey, and R. E. Lyle, *J. Amer. Chem. Soc.*, **76**, 2713 (1954).

(21) MacKenzie, *et al.*,[3] reported that this cyclohexyl homolog failed to react with methyl Grignard reagent under the conditions that they used for the cyclopentyl case.

(22) S. C. Bunce and J. B. Cloke, *J. Amer. Chem. Soc.*, **76**, 2244 (1954).

(23) S. E. Wiberley and S. C. Bunce, *Anal. Chem.*, **24**, 623 (1952).

7,7-Dicarbomethoxycycloheptatriene[1a]

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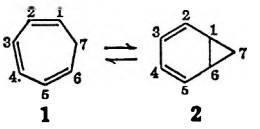
Received October 30, 1967

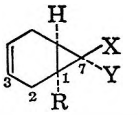
Although substitution of cyano groups at C-7 shifts the cycloheptatriene (1)–norcaradiene (2) equilibrium constant in favor of the bicyclic valency tautomer,[2] this structural feature does not seem to be required for the existence of a stable norcaradiene (*cf.* the 2,5,7-triphenyl derivative[3]). As a point on the



1 **2**

developing but still incompletely understood plot of substitution pattern *vs.* structure in this series, we record the properties of 7,7-dicarbomethoxycycloheptatriene. The syntheses of this sensitive substance and other tropilidene derivatives are carried out by methods that should be widely applicable to members of this class.

The synthetic approach to the tropilidene ring system is by cyclopropanation of a dihydrobenzene, essentially as in the method so effectively developed by Vogel and his coworkers.[4] However, the oxidation state of the resulting norcarene, which has been adjusted in previous syntheses[4] by addition of bromine to the double bond and dehydrohalogenation with amines or alcoholic alkali, involves procedures that are unsuitable to some of the cases of interest to us. For example, addition of bromine to norcarenes with a *syn*-7-carbomethoxy group leads either to complex



3a, R = H; X = Y = CO_2CH_3
b, R = CH_3; X = Y = CO_2CH_3
c, R = H; X = CN; Y = CO_2CH_3

mixtures in the case of **3a** or to a bromolactone rather than to the desired dibromide in the case of **3b**. Although a dibromide, mp 136°, can be obtained from the cyano ester **3c** with $C_5H_6N^+Br_3^-$/HOAc, dehydrohalogenation leads again to a complex mixture.

7,7-Dicarbomethoxynorcar-3-ene (**4**), prepared from the photolysis of methyl diazomalonate in 1,4-cyclohexadiene,[5] when treated with selenium dioxide in aqueous dioxane gives a mixture of the allylic alcohols **5** and **6** in the ratio 86 : 14 as determined by nuclear magnetic resonance (nmr) analysis. The same two alcohols are obtained (17 : 83 ratio) by oxidation of the isomeric diester **7**, prepared from 1,3-cyclohexadiene (see Scheme I). Although direct acid-catalyzed dehydration of these alcohols fails, conversion into bromides (PBr_3/CCl_4) and treatment with sodium methoxide gives 7,7-dicarbomethoxycycloheptatriene **8**. Dehydrogenation of **7** (with N-bromosuccinimide in CCl_4), or of **4** (with dicyanodichloroquinone in benzene), also gives **8** directly in yields of about 30%, but the substance is accompanied by unreacted starting material and aromatization product (phenylmalonic ester), from which it is difficultly separable. The method of choice in this case involves reaction of the mixture of alcohols **5** and **6** with *p*-bromobenzenesulfonyl chloride in 2,6-lutidine at 0–20°. Isolation by chromatography gives **8**, mp 45–45.5°, in yields of 25–30%. The synthesis of 3,7,7-trimethylcycloheptatriene **10**, which is much less subject than **8** to aro-

(1) (a) This work was supported in part by the National Science Foundation and the Air Force Office of Scientific Research. (b) National Institutes of Health Postdoctoral Fellow, 1966–1967.

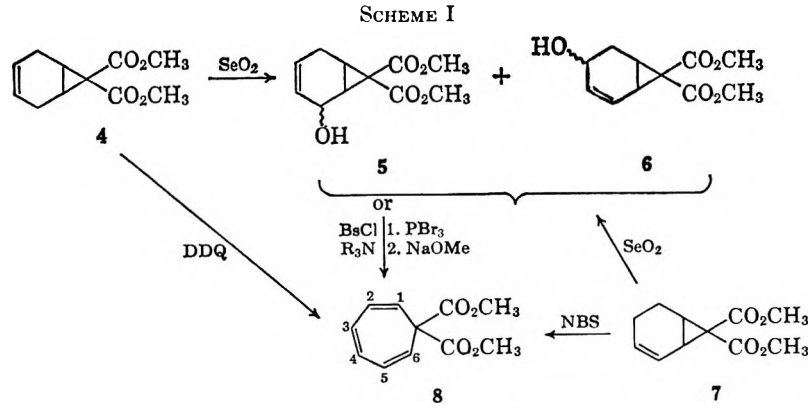
(2) E. Ciganek, *J. Amer. Chem. Soc.*, **89**, 1454 (1967).

(3) T. Mukai, H. Kubota, T. Toda, *Tetrahedron Lett.*, 3581 (1967).

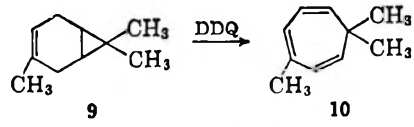
(4) E. Vogel, W. Wiedemann, H. Kiefer, and V. F. Harrison, *ibid.*, 673 (1963), and subsequent papers.

(5) For the corresponding diethyl ester, see H. Musso and U. Biethan, *Chem. Ber.*, **97**, 2282 (1964).

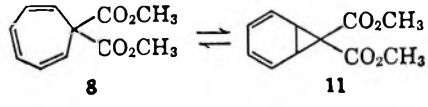
SCHEME I



matization, is accomplished in about 60% yield by the direct dicyanodichloroquinone dehydrogenation of 3-carene (**9**).



The ultraviolet spectrum [λ_{max}^{EtOH} 258 mμ (ε 3120)], of compound **8** corresponds to that of a cycloheptatriene[6] rather than a norcaradiene, for which absorptions in the regions near 235 and 275 mμ are expected.[2,7] The nmr spectrum at +35° in $CDCl_3$ shows absorptions of the C-2, C-3, C-4, and C-5 protons as a multiplet between τ 3.44 and 3.95, those of the C-1 and C-6 protons as a multiplet (broadened doublet) between 4.9 and 5.3, and those of the methoxyl protons as a singlet ($w_{1/2}$ = *ca.* 1 cps). At −35°, the methoxyl absorption remains sharp, but the separation between it and the center of gravity of the C-1–C-6 absorption decreases by about 0.2 ppm. If it is assumed that **8** and its norcaradiene valency tautomer **11** have methoxyl resonances



with fortuitously close chemical shifts, the upfield movement of the C-1–C-6 absorption at low temperature could be compatible with a small change in the composition of a rapidly interconverting equilibrium mixture of the two isomers. The possibility that the temperature effect has some other origin is the subject of a more thorough nmr study. It is already clear from the present data, however, that the substance exists largely as the cycloheptatriene **8**.[7a]

At or above 100° in $CDCl_3$ solution, **8** aromatizes to dimethyl phenylmalonate (98% yield) in a few hours. Since the most plausible mechanism for aromatization involves preliminary cycloheptatriene → norcaradiene isomerization,[6-8] the facility of aromatization of **8** compared with that of cycloheptatriene (which aromatizes very slowly below 300°) is consistent with a smaller energy difference between the norcaradiene and the cycloheptatriene forms in the dicarbomethoxy series (**8** ⇌ **11**) than in the unsubstituted (**1** ⇌ **2**) case.

Experimental Section[9]

7,7-Dicarbomethoxybicyclo[4.1.0]hept-3-ene (4).—A mixture of 17.2 g (0.109 mol) of dimethyldiazomalonate[10] and 50 g of 1,4-cyclohexadiene was diluted to 200 ml with benzene and irradiated through a Pyrex filter with a 450-W Hanovia ultraviolet lamp for 23 hr. Chromatography on neutral alumina gave 21 g of crude product which after recrystallization from pentane gave 16.5 g of material of mp 66–67°. The nmr spectrum showed absorptions for vinyl protons (2 H) at τ 4.66 (broad singlet), *exo*- and *endo*-carbomethoxy protons (6 H) as sharp singlets at 6.35 and 6.45, respectively, methylene protons at 7.55 (broad singlet), and bridgehead protons at 8.13 (broad singlet).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.00; H, 6.64.

7,7-Dicarbomethoxybicyclo[4.1.0]hepten-2-ene (7) was prepared in a similar manner from 1,3-cyclohexadiene. It had mp 40–42° (pentane). The nmr spectrum showed absorptions for vinyl protons (2 H) at τ 4.08 to 4.67 (complex quartet), *exo*- and *endo*-carbomethoxy protons as sharp singlets at 6.40 and 6.45 (6 H), and methylene and bridgehead protons at 7.58–8.52 (broad multiplet, 6 H).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.88; H, 6.74.

7,7-Dicarbomethoxybicyclo[4.1.0]hept-3-en-2-ol (5).—To a solution of 4.00 g (19.0 mmol) of 7,7-dicarbomethoxybicyclo-[4.1.0]hept-3-ene in 40 ml of 50% aqueous dioxane was added dropwise over a period of 90 min a solution of 2.23 g (20.0 mmol) of selenium dioxide in 30 ml of 50% aqueous dioxane. The mixture was stirred at 83° for 20.5 hr, cooled, filtered, diluted with ether, and washed with water. The ether layer was dried over sodium sulfate, and the solvent was removed to give 3.99 g of a viscous yellow oil. Chromatography on 120 g of Woelm basic alumina (activity IV) gave 1.45 g of a mixture of allylic alcohols (40% yield based on 600 mg of starting material recovered) which nmr analysis showed to consist of 14% 7,7-dicarbomethoxybicyclo[4.1.0]hept-2-en-4-ol (**6**) and 86% of 7,7-dicarbomethoxybicyclo[4.1.0]hept-3-en-2-ol (**5**). Repeated chromatography on alumina separated the two isomers, the Δ^2-alcohol (**6**) emerging first.

The Δ^3-alcohol **5** (probably a mixture of C-2 epimers), after bulb-to-bulb distillation at 135° (0.2 mm), showed nmr absorptions for vinyl protons (2 H) at τ 4.44 (broad singlet), α-hydroxyl proton (1 H) at 5.57, *exo*- and *endo*-carbomethoxy protons (6 H) at 6.31 and 6.42 (sharp singlets), methylene protons (2 H) at 7.43, and bridgehead protons (2 H) at 8.00.

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.31; H, 6.36.

7,7-Dicarbomethoxybicyclo[4.1.0]-hept-2-en-4-ol (6) was prepared in a similar manner from **7**. The mixed allylic alcohols

(6) *Cf.* J. A. Berson and M. R. Willcott, III, *J. Amer. Chem. Soc.*, **88**, 2494 (1966), and references cited there.

(7) J. A. Berson, P. W. Grubb, R. A. Clark, D. R. Hartter, and M. R. Willcott, III, *ibid.*, **89**, 4076 (1967).

(7a) NOTE ADDED IN PROOF.—H. Günther and M. Görlitz, University of Cologne, have carried out a low-temperature study of the nmr spectrum which permits direct observation of both isomers. At −139°, the interconversion is slow enough to prevent averaging of the chemical shifts. Details will be given in a separate paper by these authors, to whom we are indebted for advance information.

(8) W. G. Woods, *J. Org. Chem.*, **23**, 110 (1958).

(9) Nmr spectra were taken in CCl_4 or $CDCl_3$ solutions with the Varian A-60-A or HA-100 instruments. Chemical shifts are relative to internal tetramethylsilane at τ 10.00. Microanalyses are by Spang Microanalytical Laboratories.

(10) M. Regitz, *Chem. Ber.*, **99**, 3128 (1966).

(24% yield based on recovered starting material) consisted of a 17:83 mixture of 5 and 6 from which 6 was isolated by chromatography. Its nmr spectrum showed absorption for vinyl protons at τ 3.92–4.57 (2 H) as an AB quartet, α-hydroxy proton (1 H) at 6.2, carbomethoxy protons at 6.32 and 6.37 (6 H) as sharp singlets, and methylene and bridgehead protons as a broad multiplet from 7.1 to 8.5.

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.55; H, 6.36.

7,7-Dicarbomethoxycycloheptatriene (8).—To a mixture of the allylic alcohols (1.34 g, 5.90 mmol, 80% 5 and 20% 6) dissolved in 20 ml of dry 2,6-lutidine was added dropwise at 0° a solution of 4.50 g (17.7 mmol) of *p*-bromobenzenesulfonyl chloride in 5 ml of 2,6-lutidine. After 20 hr at room temperature, the mixture was treated with 20 ml of water and extracted with ether. The extract was washed successively with 10% hydrochloric acid, water, and sodium bicarbonate solution, dried over sodium sulfate, and evaporated to give 692 mg of a viscous yellow oil. Chromatography on 20 g of Woelm basic alumina (activity IV) gave a total of 387 mg of partially crystalline material which consisted mainly of 8 contaminated with a few per cent of dimethyl phenylmalonate. Recrystallization from pentane–ether gave 322 mg of colorless prisms, mp 45–45.5°. The yield based on starting material (112 mg recovered) was 28%.

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.54; H, 5.87.

The 60-Mc nmr spectrum in CCl_4 showed the C-2, C-3, C-4, and C-5 protons as a multiplet from τ 3.44 to 3.95, the C-1 and C-6 protons as an unresolved doublet from 4.90 to 5.30, and the six carbomethoxy protons as a sharp singlet at 6.37. The spectrum at −35° is described in the discussion section.

3,7,7-Trimethylcycloheptatriene was formed when 1.3 g (9.9 mmol) of 3-carene was added to a solution of 2.27 g (10 mmol) of dichlorodicyanoquinone in 10 ml of dry ether, and the mixture was heated at reflux for 30 min. Ether was removed on a rotary evaporator. Pentane was added to the residue, the precipitated solid was filtered off and extracted with pentane in a soxhlet, and the filtrate was evaporated to give 0.83 g of material which nnr analysis showed to be about 90% 3,7,7-trimethylcycloheptatriene 10 contaminated with some 3-carene. Vapor chromatographic isolation gave pure 10, which had an infrared spectrum identical with that of an authentic sample.[6]

Registry No.—**4**, 15833-41-7; **5**, 15833-42-8; **6**, 15833-43-9; **7**, 15833-44-0; **8**, 15833-45-1.

β,γ-Unsaturated Acids and Esters by Photochemical Isomerization of α,β Congeners[1,2]

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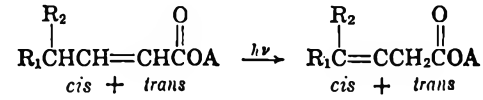
Received August 24, 1967

β,γ-Unsaturated acids and esters have been less readily available than their α,β-unsaturated relatives, for which several convenient methods of synthesis are available.[5,6] Although it is well known that β,γ isomers can be brought into equilibrium with their α,β congeners by catalysis with acid or base,[7] this method is based on thermodynamic control and suffers as a general synthetic method from wide variability with structure of the maximum attainable yield.

As a partial solution to the problem of synthesizing β,γ-unsaturated acids, we offer the photochemical isomerization of *acyclic* α,β-unsaturated acids or esters. This method is analogous to the related isomerization of α,β-unsaturated ketones and aldehydes.[8–12] The work also finds close parallels in the photochemical studies on the ionones[11] and in studies of the photochemical behavior of certain conjugated esters by Jorgenson.[13]

The conjugated acids and esters shown in Scheme I were irradiated as 2–5% solutions in saturated hydrocarbons, methanol, or in ethyl acetate with an unfiltered 450-W Hanovia Type L lamp. Although the maximum absorption of the conjugated derivatives lies about 210 nm, there is still adequate absorption at 253.7 nm mercury line to permit the isomerization. With a Pyrex filter, which absorbs irradiation below 300 nm, there is no isomerization. Typical results are shown in Table I.

SCHEME I



Compound	R_1	R_2	A
1	CH_3	CH_3	C_2H_5
2	CH_3	H	CH_3
3	H	H	CH_3
4	n-C_6H_{13}	H	H
5	n-C_7H_{15}	H	H
6	n-$C_{12}H_{25}$	H	H

TABLE I

IRRADIATION OF α,β-UNSATURATED ACIDS AND ESTERS

Compd	Reacn time, hr	Solvent	*cis/trans*	% yield[a]
1	5	Pentane		85
2	5	Pentane	*b*	85
3	12	Pentane		20[c]
4	18	Pentane	0.5	94
5	18	Hexane	0.5	95[d]
6	18	Hexane	0.5	95[d,e]

[a] Based on starting material (% conversion). [b] Not determined. [c] Remaining material isolated as 50% methyl crotonate and 30% methyl isocrotonate. [d] Also carried out in methanol with similar results. [e] This experiment was conducted by Dr. S. Safe and is included here with his generous permission.

(1) Taken in part from the dissertation of R. R. Rando submitted in partial fulfillment of the requirements for the Ph.D. Degree, Yale University, Dec 1966.

(2) This work was supported in part by Research Grant GP-0959 to Yale University by the National Science Foundation.

(3) R. R. Rando expresses his gratitude to the National Institutes of Health for the award of a predoctoral fellowship, 1963–1966, and a postdoctoral fellowship (Harvard University), 1966–1967.

(4) Where inquiries should be addressed.

(5) E. H. Rodd, Ed., "Chemistry of Carbon Compounds," Vol. 1, Elsevier Publishing Co., Amsterdam, 1951, pp 624–626; W. S. Johnson, *Org. Reactions*, **1**, 252 (1942).

(6) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

(7) See, for example, E. Boorman and R. P. Linstead, *J. Chem. Soc.*, 258 (1935), and earlier references, or G. Kon, R. P. Linstead, and G. Maclennen, *ibid.*, 2454 (1932).

(8) N. C. Yang and M. J. Jorgenson, *Tetrahedron Lett.*, 1203 (1964).

(9) H. Wehrli, R. Wenger, K. Schaffner, and O. Jeger, *Helv. Chim. Acta.*, **46**, 678 (1963).

(10) C. A. McDowell and S. S. Sifniades, *J. Amer. Chem. Soc.*, **84**, 4606 (1962).

(11) M. Mousseron-Canet, M. Mousseron, and P. Legendre, *Bull. Soc. Chim. Fr.*, 1509 (1961).

(12) K. J. Crowley, R. A. Schneider, and J. Meinwald, *J. Chem. Soc., Sect. C*, 571 (1966).

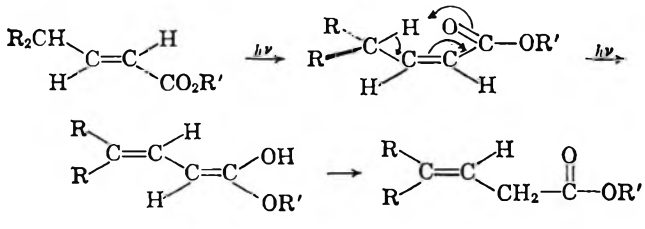
(13) M. J. Jorgenson, *Chem. Commun.*, 137 (1965).

The reaction proceeded approximately twice as rapidly in methanol as in the hydrocarbon solvents. In cases where *cis,trans* mixtures of the products were formed it was found that the esters could easily be separated by preparative tlc on $AgNO_3$–SiO_2 plates using 1% ether–hexane as the eluent. Since relatively large amounts of the *cis* products are formed, this synthetic route affords a reasonable method for obtaining the *cis* as well as the *trans* isomers.

Upon work-up virtually no remaining conjugated α,β-unsaturated isomers can be detected. When ethyl acetate was used as the solvent, not even trace amounts of the conjugated isomers could be detected (<0.1%) when the reaction was completed. Ethyl acetate, of course, filters out any light that the β,γ isomers might absorb. The high yield of unconjugated isomers depends on the fact that the integrated absorption of the unconjugated isomers above 200 nm is essentially zero while that of the conjugated isomers, if weak by customary standards, is much greater.[14]

In a reasonable mechanism, similar to that proposed by Yang and Jorgenson[8] for the photochemical isomerization of α,β-unsaturated ketones, it is hypothesized that the γ-hydrogen atom migrates to the carbonyl oxygen by means of an intramolecular, pseudo-cyclic transition state. This hypothesis requires the availability of the *cis*-geometrical isomer. That this requirement can be satisfied photochemically is shown in the study of ethyl 4-methyl-2-pentenoate, in which photochemical interconversion of the *trans* and *cis* isomers occurs more rapidly than the formation of the β,γ

SCHEME II



isomer. Scheme II illustrates only the type of geometrical requirement imposed on the reaction. Whether a two-electron concerted process or a radical intermediate is involved is not known.

This hypothesis leads to the prediction that examples in which a prior isomerization of *trans* isomer to *cis* is hindered or impossible, the reaction should proceed at a very slow rate, if at all. This prediction is borne out in an experiment in which methyl 1-cyclohexenecarboxylate is found to be completely inert to photoisomerization. In this system a *cis* transition state would require the introduction of a prohibitively strained *trans* double bond into a six-membered ring. How inviolate this restriction will turn out to be must await further testing. It should be pointed out that the restriction does not appear to apply to α,β-unsaturated ketones; at least not in the example uncovered by Wehrli, *et al.*[9]

(14) H. H. Jaffé and M. Orchin, "Theory and Practice of Ultraviolet Spectroscopy," John Wiley and Sons, Inc., New York, N. Y., 1962, pp 218–219.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer. Nmr spectra were recorded on a Varian Model A-60 analytical nmr spectrometer. The spectra were taken in carbon tetrachloride solutions. The *cis,trans* mixtures of the β,γ-methyl esters were separated by preparative tlc on 10% silver nitrate–Adsorbosil I (SiO_2) with 1% ether–hexane as the eluent. Excellent separations of the conjugated from the nonconjugated esters could be effected with either a 5-ft, 20% silicon oil column (SF 96) on 60–80 mesh firebrick or on a 4-m, 15% diethylene glycol succinate on a 40–60 mesh Kieselguhr column. As the reaction times and work-up procedures utlized in the preparations of the 3-decenoic acids, 3-undecenoic acids, and 3-hexadecenoic acids were identical, only one procedure is included. The photolyses were conducted with an unfiltered Hanovia Type L lamp at room temperature. It should be noted that the reaction times are quite dependent on the age of the lamp in use. For example, *trans*-2-decenoic acid could be completely converted into the Δ^3 isomers in 2 hr with a brand new lamp.

Photolyses. A. Ethyl 4-Methyl-2-pentenoate.—A mixture of the *cis* and *trans* isomers (*trans* predominant) was synthesized by the method of Wadsworth and Emmons.[6] The esters (1.5 g, 0.011 mol) were dissolved in 125 ml of pentane in a 150-ml Pyrex well. A Hanovia quartz immersion well with a Type L lamp was set in place and the photolysis was commenced at room temperature. An aliquot of the reaction mixture was removed after 2 hr of reaction time and analyzed by glpc (silicon oil column, column temperature = 120°). A striking buildup of the *cis* conjugated ester was observed to occur. The reaction was terminated after a total of 5 hr of reaction time. The pentane was removed affording 1.3 g (86% of theoretical yield) of a liquid whose nmr and infrared spectra completely identified it as the β,γ-unsaturated ester. Distillation of this material afforded 1.2 g of the ester without leaving behind noticable polymeric residue. The reaction product was shown to be homogeneous by glpc analysis. The compound showed infrared absorption at γ_{CCl_4}, 738 cm^{-1} and nmr absorption at 8.28 (s of relative area 3), 8.40 (s of relative area 3), 4.75 (m of relative area 1), and 7.1 ppm (d of relative area 2) on the τ scale.

B. Methyl 2-Pentenoate.—A synthetic mixture of *cis*- and *trans*-methyl 2-pentenoate[6] was photolyzed as described above to afford the methyl 3-pentenoates in the yield reported. The products were identified by their nmr and infrared spectra: γ_{CCl_4}, 3040, 1740 cm^{-1}; nmr bands, 4.3 (m of relative area 2), 6.37 (s of relative area 3), 7.1 (m of relative area 2), and 8.32 ppm (m of relative area 3).

C. Methyl Crotonate.—Methyl crotonate (2.5 g, 0.025 mol) was dissolved in 220 ml of dry pentane and photolyzed in the normal manner for 12 hr.[15] The pentane was removed leaving 2.1 g (0.021 mol) of a faint yellow liquid. Vapor phase chromatography of this material on the silicon oil column showed the presence of three compounds isolated in the ratios of 2.5:1.4:1.0. The major product proved to be the unreacted starting material. The intermediate proved to be the *cis* isomer, methyl isocrotonate, and the minor product proved to be the β,γ-unsaturated isomer, methyl 3-butenoate. Methyl isocrotonate was identified by comparison with authentic material, whereas methyl 3-butenoate was identified by its infrared and nmr spectra: γ_{CCl_4}, 1745 cm^{-1}; nmr, 4.3 (m of relative area 1), 4.8 (m of relative area 1), 5.05 (m of relative area 1), 6.4 (s of relative area 3), and 7.1 ppm (d of relative area 2).

D. Methyl 1-Cyclohexenecarboxylate.—Methyl 1-cyclohexenecarboxylate was synthesized by the method of Fichter and Simon.[16] Photolysis of the ester (3.0 g, 0.021 mol) in 220 ml of pentane in the usual manner for 7 hr afforded 2.8 g, 0.02 mol of starting material as deduced from its homogeneity on the silicon oil and diethylene glycol succinate columns and its infrared and nmr spectra.

E. *trans*-2-Decenoic Acid.—Commercial *trans*-2-decenoic acid (Aldrich Chemical Co.) (4.0 g, 0.021 mol) was dissolved in 220 ml of pentane and photolyzed in the usual manner for 18 hr. Removal of the solvent afforded 3.95 g of a colorless oil whose nmr and infrared spectra identified it as being the β,γ-unsaturated ester(s). An aliquot of this material was esterified with diazomethane. The methyl esters were analyzed on the silicon oil

(15) P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 3222 (1967).
(16) F. Fichter and C. Simon, *Helv. Chim. Acta*, **17**, 1218 (1934).

column at column temperature of 120°. One major peak was observed having the same retention time as an independently synthesized mixture[17,18] of the *cis*- and *trans*-β,γ esters. A peak amounting to 1% of the β,γ peak was also observed having the same retention time as the *trans*-α,β ester. When the photolysis was run in ethyl acetate this peak was not observed. That the main peak was indeed a mixture of the *trans*- and *cis*- β,γ isomers was shown by preparative tlc on $AgNO_3$–SiO_2 eluting several times with 1% ether–hexane. The *trans*-β,γ predominated by a factor of 2 over the *cis* and traveled closest to the solvent front. Both isomers were identified by comparing their infrared spectra with those of authentic samples, prepared independently.

Registry No.—**1** (*cis*), 15790-85-9; **1** (*trans*), 15790-86-0; **2** (*cis*), 15790-87-1; **2** (*trans*), 15790-88-2; **3** (*cis*), 4358-59-2; **3** (*trans*), 623-43-8; **4** (*cis*), 15790-91-7; **4** (*trans*), 334-49-6; **5** (*cis*), 15790-93-9; **5** (*trans*), 15790-94-0; **6** (*cis*), 2825-68-5; **6** (*trans*), 929-79-3.

(17) M. Newman and J. J. Wotiz, *J. Amer. Chem. Soc.*, **71**, 1292 (1949).
(18) R. P. Linstead, E. G. Noble, and E. J. Boorman, *J. Chem. Soc.*, 557 (1933).

A Concomitant Ethinylation and Esterification Reaction

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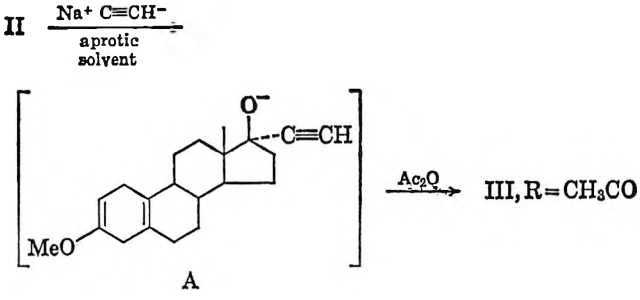
Received September 8, 1967

The preparation of 10β-hydroperoxy steroids, such as 10β-hydroperoxy-17α-ethinyl-17β-hydroxy-4-estren-3-one (I, R = H), has been reported from these laboratories.[1] Tests in rats have shown that I (R = H) is a potent contraceptive agent acting by a novel biological mechanism.[2] In view of the marked anticonception activity ascribed to ethynodiol diacetate (VI)[3] and ethindrone acetate (V, R = CH_3CO),[4] both containing a 17β-acetoxy function, it was decided to prepare the ester analog of I (R = H).

The process used for the preparation of I (R = H) (see Scheme I) was considered to be adaptable for the preparation of I (R = CH_3CO). However, neither 3-methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol (III, R = H) nor 17α-ethinyl-17β-hydroxy-5(10)-estren-3-one (IV, R = H) were found to be useful substrates for acetylation. Although the 17β-tertiary hydroxy was relatively easily esterifiable by hot acetic anhydride[5] or by acetic anhydride with acid catalysis,[6] the reactive 3-keto-$\Delta^{5(10)}$ system in IV (R = H), essential for the hydroperoxidation, and the diene system in III (R = H) underwent unwanted isomerization.[7]

Accordingly, we chose to investigate alternate procedures in the sequence for the formation of the 17β-acetoxy,17α-ethinyl moiety.

The formation of this moiety during the ethinylation reaction of the ketone II appeared possible since an oxyanion may be considered to be a generated species and might be available for rapid acylation.



Various solvent systems are known for carrying out the ethinylation of ketones; these include liquid ammonia and *t*-butyl alcohol. We considered that a preferred solvent system would be one wherein the availability of protons was low or nonexistent so that the solvent would react at a slow rate, if at all, with the esterification reagent and discharge at a slow rate, if at all, the oxyanion of "A." Dimethylformamide was considered to be such a solvent.[8]

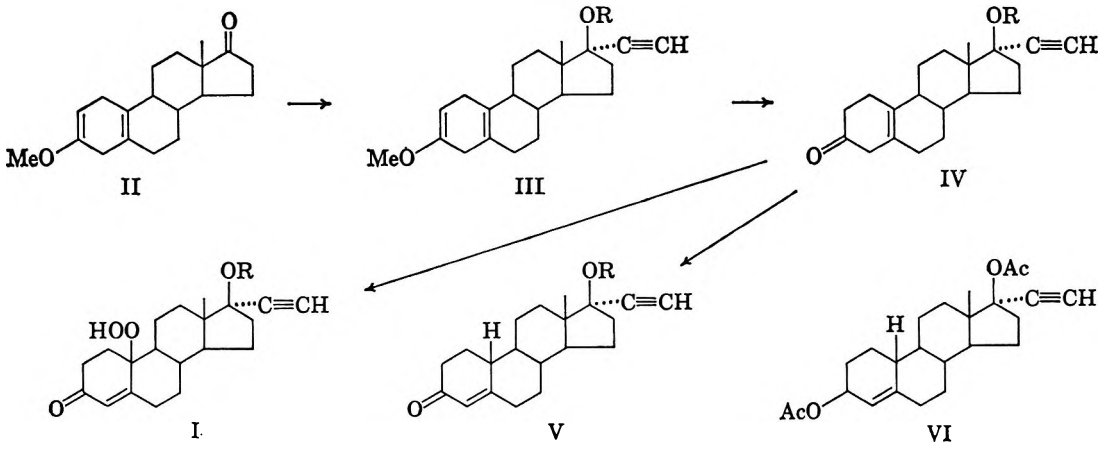
Accordingly, II was treated with sodium acetylide[9] in dimethylformamide at room temperature. After 15 min, acetic anhydride was added to the reaction medium. After an additional minute, isolation of the reaction product afforded an excellent yield of 3-methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol 17-acetate (III, R = CH_3CO). This concomitant esterification could also be accomplished with tetrahydrofuran as the solvent.[10] In our opinion, this method constitutes a facile procedure for the esterification of the important steroid hormone class which bears the 17β-OH-17α-alkinyl grouping.

Proof of structure of III (R = CH_3CO) was effected by conversion of III (R = CH_3CO) with oxalic acid into 17α-ethinyl-17β-hydroxy-5(10)-estren-3-one 17-acetate (IV, R = CH_3CO) which then, with hydrochloric acid, was converted into the known 17α-ethinyl-17β-hydroxy-4-estren-3-one 17-acetate (V, R = CH_3CO).[11]

In view of the ready esterification *via* the presumed species "A," it was felt that this same species could also be made available for esterification by base treatment of III (R = H). However, when III (R = H) was treated with potassium *t*-butoxide in dimethylformamide and then with acetic anhydride, the ethinyl

(1) (a) E. L. Shapiro, T. Legatt, and E. P. Oliveto, *Tetrahedron Lett.*, 663 (1964); (b) U. S. Patent 3,280,157 (Oct 18, 1966).
(2) (a) A. S. Watnick, J. Gibson, M. Vinegra, and S. Tolksdorf, *J. Endocrinol.*, **33**, 241 (1965); (b) A. S. Watnick, S. Tolksdorf, J. Kosierowski, and I. A. Tabachnick, Excerpta Medica International Congress Series No. III, IInd International Congress on Hormonal Steroids, Milan, May 23–28, 1966, Paper No. 123.
(3) G. Pincus, C. R. Garcia, M. Paniagua, and J. Shepard, *Science*, **138**, 439 (1962).
(4) E. Meers, *Intern. J. Fertility*, **9**, 1 (1964); H. C. Walser, R. R. Margulis, and J. E. Ladd, *ibid.*, **9**, 189 (1964).
(5) (a) L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937); (b) C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 185 (1943). In these references the configuration of the hydroxy function is β.
(6) I. Iriate, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 436 (1959).
(7) The formation of III (R = CH_3CO) from III (R = H) using acetic anhydride and pyridine is reported in British Patent 922,877 (April 3, 1963), although no physical constants are noted. In our hands the procedure was unsatisfactory because of substantial loss of the diene system in ring A.
(8) C. Burgess, D. Bunn, P. Feather, M. Howarth, and V. Petrow [*Tetrahedron*, **22**, 2829 (1966)] report etherification with methyl iodide in a sodamide–liquid ammonia medium.
(9) J. A. Campbell, J. C. Babcock, and J. A. Hogg, *J. Amer. Chem. Soc.*, **80**, 4717 (1958).
(10) We wish to thank R. Grocela and N. Murrill of the Process Research Development Department for carrying out this experiment.
(11) Compare ref 6, wherein V (R = CH_3CO) was prepared from V-(R = H) by acid esterification to 17α-ethinyl-3,5-estradiene-3,17-diol 3,17-diacetate followed by acid hydrolysis.

SCHEME I



moiety present in III (R = H) was extruded, and an excellent yield of the 17-ketone II was obtained.[12]

The β,γ-unsaturated ketone IV (R = CH_3CO), which had been obtained by oxalic acid hydrolysis of the 17-acetate III (R = CH_3CO), was converted by oxygenation into 17α-ethinyl-17β-hydroxy-10β-hydroperoxy-4-estren-3-one 17-acetate (I, R = CH_3CO), and thus our principal objective was attained.

Experimental Section[13]

3-Methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol 17-Acetate (III, R = CH_3CO). A.—3-Methoxy-2,5(10)-estradien-17-one (II) (40 g) was dissolved in 800 ml of dimethylformamide and stirred under an argon atmosphere. To the reaction mixture was added 13.41 g of sodium acetylide (2 equiv; 74.5 ml of 18% sodium acetylide[14] in xylene from which the xylene was partially removed by centrifugation), and the reaction was stirred at room temperature, under argon, for 15 min. With rapid agitation, 19.78 ml of acetic anhydride (1.5 equiv) was added and stirred for 1 min. The reaction mixture was poured into 8 l. of water containing 240 g of sodium chloride, and the resulting mixture was rapidly agitated for 2 hr; the precipitate was then separated by filtration and air dried to yield a solid which consisted essentially of III (R = CH_3CO) as measured by tlc (silica gel, chloroform–benzene 3:1). Crystallization from methanol–water containing a trace of pyridine yielded 21 g of a yellow solid, mp 160–165°. Recrystallization from methanol–water–pyridine afforded the analytical sample: mp 167–170°; $[\alpha]D$ +58°; nmr, δ (ppm) (TMS = 0) 0.85 ($C_{13}CH_3$), 1.98 ($C_{17}OCOCH_3$), 3.48 (C_3OCH_3 plus CH_3OH), 3.71 (C≡CH), 4.68 (C_2H); λ_{max} 3.08, 5.74, 5.90, 6.01, 7.94, and 8.20 μ; λ_{max} end absorption only; $\lambda_{max}^{aqueous\ HCl-MeOH}$ 239 mμ (ϵ 16,600).

Anal. Calcd for $C_{23}H_{30}O_3 \cdot {}^1/_4CH_3OH$: C, 77.03; H, 8.62. Found: C, 77.23, 76.91; H, 8.48, 8.36.

B.—To a solution of 20 g of II in 200 ml of tetrahydrofuran was added 200 ml of a suspension of 18% sodium acetylide in xylene. The reaction mixture was agitated at 25° for 4 hr. An aliquot of 12 ml (approximately 600 mg of steroid) was then removed, mixed with 1.6 ml of acetic anhydride, and stirred at room temperature for 15 min. After pouring into ice water and extracting with methylene chloride, there was obtained 700 mg of crude product, the major component exhibiting the same migration rate as III (R = CH_3CO) by tlc (silica gel, hexane–acetone 7:3). Crystallization from aqueous methanol (with trace of pyridine) gave III (R = CH_3CO), comparison with product from A by infrared and nmr spectra and tlc.

17α-Ethinyl-17β-hydroxy-5(10)-estren-3-one 17-Acetate (IV, R = CH_3CO).—To a suspension of 19 g of 3-methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol 17-acetate (III, R = CH_3CO) in 1625 ml of methanol and 325 ml of water was added 19 g of oxalic acid. The reaction mixture was stirred at room temperature for 1.75 hr (solution occurring at 1.25 hr) and then poured into 16 l. of water. The insolubles were collected by filtration, washed with water, and dried in air at 30° to yield 15 g of solid which was principally one component as measured by tlc (silica gel, $CHCl_3$). This solid exhibited no absorption in the ultraviolet from 220–350 mμ at approximately 0.0025% concentration, the significant infrared absorption bands being λ_{max} 3.04, 5.72, 5.82, 8.02, and 8.15 μ. This solid was used in the next step because attempted purification by crystallization or silica gel column chromatography was unsuccessful.

17α-Ethinyl-17β-hydroxy-4-estren-3-one 17-Acetate (V, R = CH_3CO). A. From 17α-Ethinyl-17β-hydroxy-5(10)-estren-3-one (IV, R = H).—A solution consisting of 1 g of 17α-ethinyl-17β-hydroxy-5(10)-estren-17β-ol-3-one (IV, R = H), 1.25 ml of concentrated hydrochloric acid, 180 ml of methanol, and 20 ml of water was refluxed for 0.5 hr. The reaction mixture was then diluted with 1.5 l. of water to give a precipitate which was collected by filtration and dried. This solid of V (R = H) was dissolved in 3 ml of glacial acetic acid and 1 ml of trifluoroacetic anhydride, and allowed to stand at room temperature for 0.5 hr. The reaction mixture was poured into 50 ml of water, filtered, and twice crystallized from acetone–hexane to yield 17α-ethinyl-17β-hydroxy-4-estren-3-one 17-acetate (V, R = CH_3CO): mp 161–163°; $[\alpha]D$ ($CHCl_3$) −30.3°; λ_{max} 239 mμ (ϵ 16,900) [lit.[11] mp 161–162°; $[\alpha]D$ ($CHCl_3$) −33°; $\lambda_{max}^{95\%\ EtOH}$ 240 mμ (log ϵ 4.20)]; λ_{max} 3.08, 4.72, 5.72, 6.01, 6.19, 8.01, 8.10, 8.20, and 11.22 μ.

B. From 17α-Ethinyl-17β-hydroxy-5(10)-estren-3-one 17-Acetate (IV, R = CH_3CO).—A mixture of 1 g of 17α-ethinyl-17β-hydroxy-5(10)-estren-3-one 17-acetate (IV, R = CH_3CO), 1.25 ml of concentrated hydrochloric acid, 180 ml of methanol and 20 ml of water was brought to reflux and allowed to cool to room temperature over a 2.5-hr period. The reaction mixture was poured into 1.5 l. of water, and the resulting solid collected by filtration, dried, and twice crystallized from isopropyl ether to yield V (R = CH_3CO): mp 157–161° [mixture melting point with V (R = CH_3CO) from A 157–161°]; $[\alpha]D$ (CH_3Cl_3) −26.8°; λ_{max} 239 mμ (ϵ 16,300); infrared identical with V (R = CH_3CO) from A.

10β-Hydroperoxy-17α-ethinyl-17β-hydroxy-4-estren-3-one 17-Acetate (I, R = CH_3CO).—Oxygen was slowly bubbled through a solution of 2 g of 17α-ethinyl-17β-hydroxy-5(10)-estren-3-one 17-acetate (IV, R = CH_3CO) in a mixture of 36 ml of carbon tetrachloride and 18 ml of hexane while irradiating with fluorescent light. At 18 hr a yellow oily solid was removed and the oxygenation continued. At 90 hr a white solid (640 mg, 1 spot tlc, silica gel, 3:1 $CHCl_3$–EtOAc) was collected and crystallized from methanol–water to yield 10β-hydroperoxy-17α-ethinyl-17β-hydroxy-4-estren-3-one 17-acetate (I, R = CH_3CO): posi-

(12) De-ethination to the 17-ketone has been effected (a) with boiling aqueous alkali by H. Langecker [*Naturwissenschaften*, **46**, 601 (1959)] and (b) with potassium *t*-butoxide in *t*-butyl alcohol as cited by H. Ringold in "Mechanism of Action of Steroid Hormones," C. A. Villee and L. L. Engle, Ed., Pergamon Press Inc., New York, N. Y., 1961, p 218.

(13) Melting points were determined on a Kofler block and are uncorrected. Nmr spectra were measured with a Varian A-60A spectrometer. Rotations are in dioxane at 25° at about 1% concentration; infrared spectra are from the solids in Nujol, and ultraviolet spectra are of methanol solutions unless otherwise stated.

(14) Air Reduction Company, Inc., Middlesex, N. J.

tive starch iodide test; mp 178–181°, bubbling; $[\alpha]D$ −29°; λ_{max} 233 mμ (ε 15,000); λ_{max} 3.02, 3.05, 5.69, 5.98 (shoulder), 6.02, 6.07 (shoulder), 7.95, and 8.08 μ; nmr, δ (ppm) (TMS = 0): 0.85 ($C_{13}CH_3$), 1.98 ($C_{17}OCOCH_3$), 3.47 (C≡CH), 5.88 (C_4H), 11.28 (C_{10}-O-OH).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.11; H, 7.45.

Generation of 3-Methoxy-2,5(10)-estradien-17-one (II) from 3-Methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol (III, R = H).—To a solution consisting of 0.2 g of III (R = H) in 10 ml of dimethylformamide under nitrogen was added 0.1 g of potassium *t*-butoxide. After 5 min at room temperature, 0.11 ml of acetic anhydride was added. One minute later the reaction mixture was poured into 200 ml of water. The pH was adjusted to about 3 with dilute HCl, and the insolubles, which were collected by filtration and dried at 60° under vacuum, weighed 140 mg. The infrared spectrum matched that of authentic II.

Registry No.—I (R = CH_3CO), 13236-11-8; III (R = CH_3CO), 13251-69-9; V (R = CH_3CO), 51-98-9.

Acknowledgment.—We wish to thank Mr. Milton Yudis and Mrs. Henrietta Marigliano for their aid in the nmr interpretations.

Organocadmium Reagents. V. Reaction with α-Halo Esters and Ketones[1a,b]

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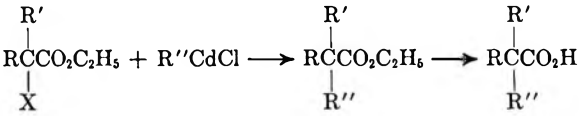
Received October 30, 1967

In view of the diminished reactivity of organocadmium compounds as compared to lithium or magnesium reagents,[2] it is attractive to consider new syntheses of compounds containing functional groups which would not survive treatment with the more reactive organometallic reagents. Since organocadmium reagents are known to displace halogens in a few instances[3] but do not appear to decompose esters,[2,4] we undertook an investigation of the behavior of some α-halogenated esters with these reagents. If displacement of halogen were to occur in preference to reaction at the ester site, the reaction would be potentially useful as a synthetic route to more complex acids and derivatives.



R, R′ = H, CH_3, $CO_2C_2H_5$
R″ = C_6H_5, α-$C_{10}H_7$

This hypothesis was borne out by experiment to a limited extent. We found the reaction to be sensitive to the structure of the halo ester, solvent, and temperature, as can be seen from the results summarized in Table I. The bromo esters of acetic and propionic acids could be converted, respectively, into arylacetic and α-arylpropionic acids in yields of 40–62% under certain experimental conditions. Bromoisobutyrate did not form displacement product in ether or THF but was recovered partially or completely. We found no trace of a Claisen product, ethyl 2,2,4-trimethyl-3-oxopentanoate, as reported by Cason and Fessenden[5] from a similar reaction with the *n*-butylcadmium reagent in benzene.

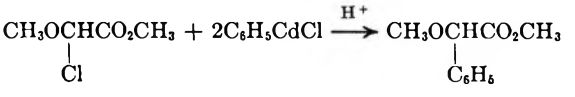
From the two chloro esters examined, only starting material, solvolysis product, or dehalogenative coupling products could be isolated.

The striking effect of solvent on the displacement was unexpected. Thus the conversion of bromoacetate into arylacetic acid was four to five times greater in THF than in ether. Under similar reaction conditions bromopropionate reacted efficiently in ether but failed completely in THF.

Optimum temperature for reactions in THF appears to depend on the cadmium reagent. Highest conversions with the phenylcadmium reagent in THF were realized at ice-bath temperature, while the α-naphthylcadmium reagent was considerably more reactive at room temperature. At least two factors may account reasonably for this temperature effect: increased coupling of phenyl reagent at the higher temperature and lower reactivity of the α-naphthylcadmium reagent, as well as its observed precipitation in THF at ice-bath temperature. By-products from the two cadmium reagents were biphenyl and naphthalene in every case, although the amounts of these hydrocarbons were not usually determined.

The reaction with α-halo ketones proceeded similarly, but the yields were generally lower than those from esters. Deoxybenzoin could be isolated only in 3–31% yield from phenacyl bromide and phenylcadmium reagent, along with the coupling products, biphenyl and 1,2-dibenzoylethane.

To our knowledge, a displacement of halogen in simple α-halo esters has not been reported up until now. Although Gross and Freiberg[4] recently effected the displacement of the chloro group in methyl chloromethoxyacetate, this substrate is both an ether and an ester; and the replacement of halogen in α-halo ethers by organocadmium reagents is well known.[3a,3b]



Of great interest is an apparent halogen–metal exchange, which occurs between diethyl bromomalonate and the phenylcadmium reagent. Both malonic ester and bromobenzene were isolated in equal amounts, roughly 75% yield. Thus the displacement method is not applicable to the synthesis of substituted malonic acids.

A similar halogen–metal exchange reaction was proposed earlier to explain Reformatsky and Claisen products from organocadmium reagents.[5]

(1) (a) Abstracted in part from the Ph.D. Thesis of J. R. Y., University of New Hampshire, 1967; (b) P. R. Jones and J. D. Young, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p S94; (c) National Defense Education Act fellow, 1963–1966.

(2) J. Cason, *Chem. Rev.*, **40**, 15 (1947); D. A. Shirley, *Org. Reactions*, **8**, 27 (1943).

(3) (a) R. K. Summerbell and L. N. Bauer, *J. Amer. Chem. Soc.*, **58**, 759 (1936); (b) C. D. Hurd and R. P. Holysz, *ibid.*, **72**, 2005 (1950); (c) R. C. Fuson, S. B. Speck, and W. R. Hatchard, *J. Org. Chem.*, **10**, 55 (1945); (d) P. Chancel, *Bull. Soc. Chim. Fr.*, 228 (1951); (e) D. V. Nightingale, W. S. Wagner, and R. H. Wise, *J. Amer. Chem. Soc.*, **75**, 4701 (1953); (f) P. R. Jones and A. A. Lavigne, *J. Org. Chem.*, **25**, 2020 (1960); (g) F. N. Jones and C. R. Hauser, *ibid.*, **27**, 3364 (1962); (h) P. R. Jones, R. G. Nadeau, and G. A. Crosby, Abstracts A of IUPAC Congress, London, 1963, p 267; (i) P. R. Jones, C. J. Jarboe, and R. Nadeau, *J. Organometal. Chem.*, **8**, 361 (1967).

(4) H. Gross and J. Freiberg, *Chem. Ber.*, **99**, 3260 (1966).

(5) J. Cason and R. J. Fessenden, *J. Org. Chem.*, **22**, 1326 (1957).

TABLE I

REACTION OF ORGANOCADMIUM REAGENTS WITH α-HALO ESTERS

Ester RC(R')(X)COOEt			Cd reagent			Reaction temperature	Yield, %
R	R'	X	R''	Ratio[a]	Solvent	(time, hr)	RC(R')(R'')COOH(C2H6)
H	H	Br	α-$C_{10}H_7$	1	Ether	Reflux (10)	16
H	H	Br	α-$C_{10}H_7$	2	THF	Ice bath (10)	9[b]
H	H	Br	α-$C_{10}H_7$	2	THF	Room temperature (8)	62
H	H	Br	C_6H_5	1	Ether	Reflux (10)	11
H	H	Br	C_6H_5	2	THF	Ice bath (10)	53, 46
H	H	Br	C_6H_5	2	THF	Room temperature (8)	26
CH_3	H	Br	C_6H_5	2	Ether	Reflux (10)	40, 58
CH_3	H	Br	C_6H_5	2	THF	Ice bath (10)	0[c], 0[d]
CH_3	CH_3	Br	C_6H_5	2	Ether	Reflux (10)	0[e]
CH_3	CH_3	Br	C_6H_5	2	THF	Ice bath (10)	0[f]
H	H	Cl	C_6H_5	2	THF	Ice bath (10)	0[g]
CH_3	H	Cl	C_6H_5	2	Ether	Reflux (10)	0[h]

[a] Molar ratio of organocadmium reagent (R''CdCl) to halo ester. [b] Naphthalene (89%) recovered. [c] Starting material recovered (50%). [d] 2,3-Dimethylsuccinic acid isolated (11%). [e] Starting materal recovered quantitatively. [f] Starting material, biphenyl, and unidentified acid obtained. [g] Starting material recovered (30%) along with biphenyl. [h] Lactic acid isolated after saponification.

$$BrCH(CO_2C_2H_5)_2 + C_6H_5CdCl \longrightarrow [ClCdCH(CO_2C_2H_5)_2] + C_6H_5Br$$

$$[ClCdCH(CO_2C_2H_5)_2] \xrightarrow{(H_2O,\ H^+)} CH_2(CO_2C_2H_5)_2$$

Sufficient experimental results are lacking at the present time to provide a meaningful evaluation of substrate, solvent, and temperature effects and their relationship to possible mechanisms for the reaction. It is hoped that forthcoming experiments will indicate whether the reaction conforms to the addition–rearrangement pathway, proposed by Ando for the analogous reaction with Grignard reagents.[6]

Observations to date, however, warrant the view that the displacement reaction with organocadmium compounds is a potentially valuable route to α-substituted acids and their derivatives from α-bromo esters where the site of displacement is primary or secondary.

Experimental Section

Infrared and nuclear magnetic resonance spectra, consistent for the compounds examined, are on file in the Department of Chemistry, University of New Hampshire. The following represent typical reaction and isolation procedures.

Preparation of the Organocadmium Reagents.—The Grignard reagent was prepared from equimolar amounts (0.1 or 0.2 mol, as noted) of magnesium and organic bromide and enough dry ether or tetrahydrofuran (THF) to make a 1.0–1.5 *M* solution. After all of the organic bromide had been added, the reaction mixture was allowed to reflux for 0.5 hr and was then filtered from excess magnesium if any remained. The cadmium reagent, assumed to be the unsymmetrical RCdCl or ArCdCl, was prepared by the addition of an equimolar portion of anhydrous cadmium chloride over a period of 15 min. When THF was the solvent, the solution of Grignard reagent was cooled to room temperature or to ice-bath temperature before addition of cadmium chloride was started. Cooling was provided during the addition. In every case a Gilman test[7] showed the absence of Grignard reagent as soon as all of the cadmium chloride had been added.

Reaction of α-Naphthylcadmium Reagent with Ethyl Bromoacetate.—To 0.2 mol of α-naphthylcadmium reagent in THF at room temperature was added 16.7 g (0.1 mol) of ethyl bromoacetate in 15 ml of THF. When about one-half of the bromo ester had been added, the mixture thickened so that stirring was difficult. The mixture was warmed only sufficiently to keep it semifluid. After 8 hr the mixture was hydrolyzed with 100 ml of 3 *N* hydrochloric acid. The organic portion was removed, concentrated, and saponified by prolonged reflux with 100 ml of 10% sodium hydroxide in 50% ethanol. The basic solution was treated with Norit, acidified with concentrated hydrochloric acid, and cooled. There was obtained 11.5 g (62%) of α-naphthylacetic acid, mp 110–120° (recrystallized from benzene–ligroin, mp and mmp 130–132°).

Reaction of Phenylcadmium Reagent with Ethyl Bromoacetate.—A solution of 16.7 g (0.1 mol) of ethyl bromoacetate in 15 ml of THF was added dropwise, with stirring, to 0.2 mol of phenylcadmium reagent in THF, which was cooled in an ice bath. After 10 hr at ice-bath temperature, the mixture was hydrolyzed with an excess of saturated ammonium chloride and then steam distilled.

A first fraction of about 150 ml contained THF exclusively; evaporation on a steam bath left no residue. About 400 ml more of distillate was collected; additional distillate contained no carbonyl compound but did contain biphenyl. By ether extraction of the second distillate there was obtained 8.6 g (53%) of ethyl phenylacetate, bp 66–71° (0.6–1.0 mm), identified by its spectra, properties, and by conversion into α-phenylacetamide, mp 154–154.5° and mmp 155–156°.

Reaction of Phenylcadmium Reagent with Diethyl Bromomalonate.—A solution of 23.9 g (0.1 mol) of diethyl bromomalonate in 25 ml of ether was added dropwise, with stirring, to 0.2 mol of phenylcadmium reagent in refluxing ether. After 10 hr at reflux the mixture was cooled in an ice bath and hydrolyzed with 100 ml of 3 *N* hydrochloric acid. The dark oil (34.1 g) obtained by ether extraction was shown to contain diethyl malonate, bromobenzene, and a trace of diethyl bromomalonate. The amount of diethyl malonate was estimated to be 12 g (75%) by nmr analysis with toluene added to the sample as a standard. Analysis of the mixture by glpc showed diethyl malonate and bromobenzene to be present in equimolar amounts. Similar results were obtained with THF as the solvent.

Registry No.—α-Naphthylcadmium reagent, 15924-34-2; phenylcadmium reagent, 15924-35-3; RC(R')(X)COOEt (R = R' = H; X = Br), 105-36-2; (R = CH_3; R' = H; X = Br), 535-11-5; (R = R' = CH_3; X = Br), 600-00-0; (R = R' = H; X = Cl), 105-39-5; (R = CH_3; R' = H; X = Cl), 535-13-7.

(6) T. Ando, *Yuki Gosei Kagaku Kyokai Shi*, **17**, 777 (1959); *Chem. Abstr.*, **54**, 4492*b* (1960).

(7) H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, **47**, 2002 (1925).

The Crystal Structure of 1,1,2,2-Tetracarbomethoxyethane. The Conformation of the Carbomethoxy Group

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Received September 28, 1967

A study of the crystal structure of dimethyl oxalate showed that the molecule is planar and that the methyl group and the carbonyl oxygen are eclipsed.[1] A comparison of these findings with results obtained in the liquid and vapor phases indicates that the most stable conformation of the ester group is generally the one in which the four atoms constituting the ester function (CO_2C) are nearly coplanar. Furthermore, the alkyl group and the carbonyl oxygen prefer to be eclipsed.[2-6] The dimer of dimethyl malonate, 1,1,2,2-tetracarbomethoxyethane, appeared to be an attractive molecule for further investigation of conformational aspects of the ester group since the ester group in this molecule is contained in an unusual molecular environment.

Crystals of the ester were grown from methanol and were obtained as hard, colorless, thick plates. The crystals selected for mounting were parallelepipeds approximately 0.5 mm wide, 0.5 mm long, and 0.4 mm thick. The X-ray data were collected around three axes using multifilm equi-inclination Weissenberg photographs with Cu Kα radiation at ambient temperatures. The crystals were stable in the X-ray beam and no decomposition was noted during the time required to collect the data. Intensities were measured by comparison of photographs with a calibrated film strip, and 1084 independent reflections were observed. Lorentz and polarization corrections were applied, interlayer scaling corrections were applied, and the data were placed on an absolute scale using Wilson's method.[7] The structure factors were then converted into E values.

The crystal data are as follows: monoclinic, mp 137.5–138.5°; $a = 6.81 \pm 0.02$, $b = 7.60 \pm 0.02$, $c = 12.44 \pm 0.02$ Å; $\beta = 107.9° \pm 0.4°$; $V = 612.6$ Å^3. The observed density (by flotation in toluene–carbon tetrachloride solution) was found to be 1.40 g/cc; the calculated value is 1.42 g/cc; $Z = 2$. From extinctions, $h0l$ absent with l odd, $0k0$ absent with k odd, the space group was determined to be $P2_1/c$.

The structure was solved by direct methods using the symbolic addition procedure.[8] Phase determination was routine and the signs of 252 reflections with E values greater than 1.0 were readily determined. An E map based on these data clearly revealed the structure. Refinement was carried out by differential syntheses with anisotropic temperature factors until R had reached a final value of 11.6% for 1084 independent reflections; hydrogen atoms were ignored throughout the calculations. All computations were carried out on an IBM 7072 computer with programs written in Professor G. A. Jeffrey's laboratory at the University of Pittsburgh.

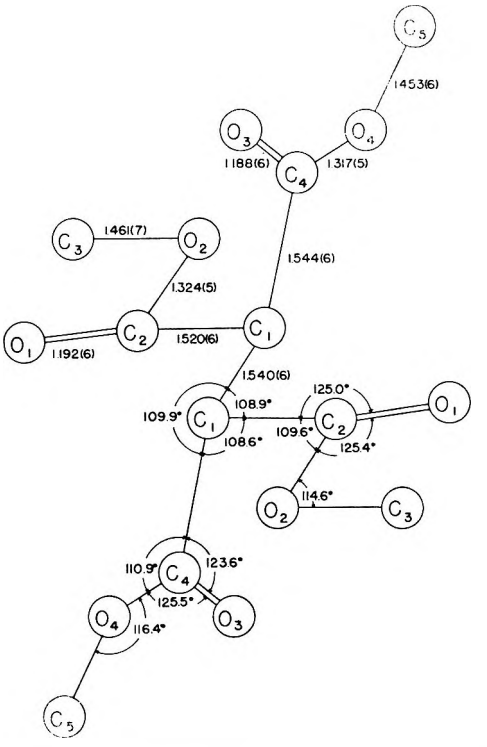


Figure 1.—1,1,2,2-Tetracarbomethoxyethane, [b] axis projection.

Results and Discussion

The molecule possesses a center of symmetry and makes use of this while crystallizing in the monoclinic space group, $P2_1/c$. Atomic coordinates with standard deviations are listed in Table I, and anisotropic thermal factors are recorded in Table II. A view of the molecule down the [b] axis is shown in Figure 1.

Least squares planes were calculated for each of the five atoms comprising the ester group in terms of orthogonal axes, X, Y, and Z'. The plane through C_1, C_2, C_3, O_1, and O_2 shows that these atoms are distributed in the plane

$$0.9117X + 0.4108Y - 0.0103Z' = 0.1230$$

with deviations of 0.008, −0.002, 0.0011, −0.003, and −0.014 Å, respectively. The five atoms of the second ester group, C_1, C_4, C_5, O_3, and O_5, also form a plane and the constants are

$$-0.5597X + 0.5676Y + 0.6038Z' = -0.3316.$$

The deviations of the atoms from this plane were −0.015, 0.006, −0.020, 0.004, and 0.025 Å, respectively.

An examination of these data indicates that both of the ester groups are planar within experimental error and that the bond distances and angles are normal. The similarity of these results with those obtained from electron diffraction studies[5] (vapor phase) and nmr and other spectroscopic investigations[2-4,6] (liquid phase) suggests that the degree of resonance interaction between the alkyl oxygen and carbonyl group is sufficiently

(1) M. W. Dougill and G. A. Jeffrey, *Acta Crystallogr.*, **6**, 831 (1953).
(2) G. J. Karabatsos, N. Hsi, and C. E. Orzech, Jr., *Tetrahedron Lett.*, 4639 (1966).
(3) J. E. Piercy and S. V. Subrahmanyam, *J. Chem. Phys.*, **42**, 1475 (1965).
(4) R. F. Curl, *ibid.*, **30**, 1529 (1959).
(5) J. M. O'Gorman, W. Shand, Jr., and V. Schomaker, *J. Amer. Chem. Soc.*, **72**, 4222 (1950).
(6) J. K. Wilmshurst, *J. Mol. Spectrosc.*, **1**, 201 (1957).
(7) A. J. C. Wilson, *Nature*, **150**, 151 (1942).
(8) I. L. Karle and J. Karle, *Acta Crystallogr.*, **16**, 969 (1963); J. Karle and I. L. Karle, *ibid.*, **21**, 849 (1966).

TABLE I
POSITIONAL PARAMETERS FOR 1,1,2,2-TETRACARBOMETHOXYETHANE

Atom	X	Y	Z
O_1	0.0167 (5[a])	−0.1817 (5)	−0.1617 (3)
O_2	0.1846 (5)	−0.3486 (4)	−0.0139 (3)
O_3	0.3568 (5)	0.1290 (4)	0.0511 (3)
O_4	0.3946 (5)	−0.0936 (4)	0.1729 (3)
C_1	0.0748 (6)	−0.0745 (6)	0.0280 (4)
C_2	0.0865 (5)	−0.2050 (5)	−0.0624 (3)
C_3	0.2102 (9)	−0.4825 (7)	−0.0928 (5)
C_4	0.2926 (6)	0.0015 (5)	0.0843 (4)
C_5	0.6058 (8)	−0.0403 (8)	0.2297 (5)

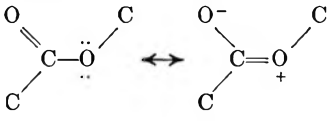
[a] Standard deviations in the least significant figures.

TABLE II
ANISOTROPIC THERMAL FACTORS[a]

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{23}	B_{13}
O_1	5.62	3.45	3.06	0.81	0.04	0.72
O_2	5.58	2.13	3.16	0.85	0.06	0.91
O_3	3.96	3.12	4.45	−0.68	0.93	0.51
O_4	3.52	3.31	3.31	−0.08	0.85	0.23
C_1	3.28	1.88	3.14	−0.22	0.01	0.54
C_2	3.20	2.38	2.85	0.04	0.09	0.31
C_3	4.40	5.14	4.43	−0.08	1.05	−0.13
C_4	6.99	2.83	4.20	1.18	−0.74	1.71
C_5	2.99	2.25	2.38	0.33	−0.01	0.58

[a] These are of the form $\exp[-(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} + 2B_{12}hka^*b^* + 2B_{23}klb^*c^* + 2B_{13}hla^*c^*)]$.

important to constrain the ester group to a planar conformation despite any unfavorable eclipsing interactions that may exist.



Registry No.—1,1,2,2 - Tetracarbomethoxyethane, 5464-22-2.

Acknowledgment.—We wish to express our gratitude to the National Science Foundation for support of C. Richard Costin during the summer as an undergraduate research participant.

The Reaction of Benzyne with Indene

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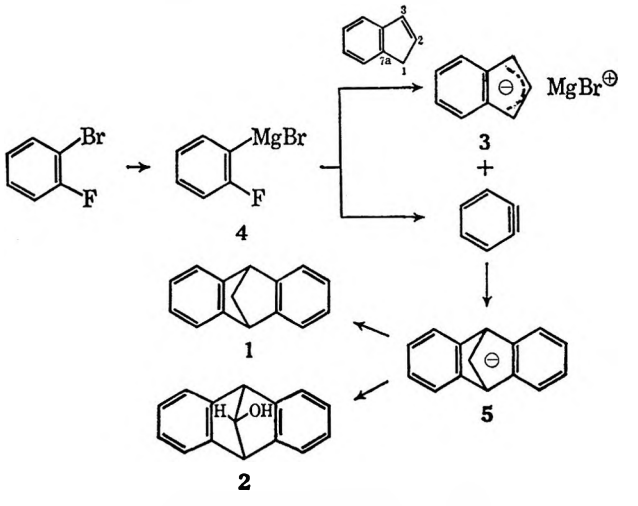
In continuation of a study on the Diels–Alder reaction of indene[1] we now wish to report on its reaction with benzyne. Indene has been shown to give various adducts in which bond formation occurs at the 2,3, at the 1,3, or at the 2,7a positions, depending on the dienophile. Benzyne reacted in the last mentioned fashion with styrene[2] and with α-methylstyrene,[3] which are formally ring-opened indenes.

When benzyne was generated *in situ* in refluxing tetrahydrofuran from *o*-bromofluorobenzene and magnesium[4] in the presence of indene, two products, a $C_{15}H_{12}$ (1) and a $C_{15}H_{12}O$ (2) species, could be isolated by thin layer chromatography. The nmr spectrum at 60 Mc of **1**, showing an A_2B_2 eight-proton signal in the aromatic region centered at 422.5 cps, a two-proton signal in the benzyl region as a very narrow triplet at 253.4 cps ($W_{1/2}$ = 4.0 cps), and a two-proton signal as a very narrow triplet at 148.7 cps ($W_{1/2}$ = 3.7 cps), indicated a symmetrical molecule. Besides the molecular ion peak of *m/e* 192, a feature of diagnostic value in the mass spectrum, was a major fragment at *m/e* 115 indicating indenyl ion (C_9H_7). These data best fit the known 9,10-dihydro-9,10-methanoanthracene (**1**)[5] whose reported melting point and ultraviolet spectrum are identical with ours. The infrared spectrum of **2** revealed the presence of a hydroxyl group at 3568 cm^{-1} and the nmr spectrum (after exchange with deuterium oxide) showed a complex eight-proton signal in the aromatic region centered at about 425, a two-proton triplet at 253, and a one-proton triplet at 262 cps. The melting point and ultraviolet spectrum of **2** are virtually identical with those reported for 9,10-dihydro-9,10-methanoanthracen-11-ol by Meinwald.[6] Identification of our substance as **2** was confirmed by comparison with an authentic sample.

A mechanism for the formation of **1** and **2** accounting for the unexpected presence of **2** could be advanced when it was found that **1** and **2** were not obtained when benzyne was generated from either benzenediazonium-2-carboxylate[7] or diphenyliodonium-*o*-carboxylate.[8] In this view, the carbanionic intermediate **3**, resulting from reaction of the acidic indene with **4**, adds to benzyne. The exact nature of this cycloaddition, whether in one or two steps, is uncertain but a carbanionic species must be involved. This is followed by reaction of the resulting **5** with water leading to **1** and with residual oxygen leading to **2**. It is generally held that organometallic compounds react with oxygen yielding alcohols *via* reduction of the intermediate hydroperoxide anion by carbanion.[9,10]



(1) C. F. Huebner, P. L. Strachan, E. M. Donoghue, N. Cahoon, L. Dorfman, R. Margerison, and E. Wenkert, *J. Org. Chem.*, **32**, 1126 (1967).
(2) W. L. Dillon, *Tetrahedron Lett.*, 939 (1966).
(3) E. Wolthuis and W. Cady, *Angew. Chem. Intern. Ed. Engl.*, **6**, 555 (1967).
(4) N. Rabjohn, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 965.
(5) W. R. Vaughan and M. Yoshimine, *J. Org. Chem.*, **22**, 7 (1957).
(6) J. Meinwald and E. G. Miller, *Tetrahedron Lett.*, 256 (1961). We are indebted to Professor Meinwald for a sample of **2**.
(7) L. Friedman and F. M. Logullo, *J. Amer. Chem. Soc.*, **85**, 1549 (1963).
(8) L. F. Fieser, "Organic Experiments," D. C. Heath and Co., Boston, Mass., 1965, p 312.
(9) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, p 344.
(10) E. Müller and T. Topel, *Ber.*, **72**, 273 (1939).

It is known that organometallic compounds react with benzyne.[11] Wittig[12] has shown that benzyne generated from *o*-bromofluorobenzene adds to cyclopentadiene in Diels–Alder fashion to give 1,4-dihydro-1,4-methanonaphthalene. Indene is thought to add 1,3 to maleic anhydride *via* the reactive entity, isoindene (6).[13] However, since this occurs only at temperatures in the vicinity of 200°,[14] the reaction of benzyne with indene at 65° would not appear to be of this nature.

Experimental Section[15]

9,10-Dihydro-9,10-methanoanthracene (1) and 9,10-Dihydro-9,10-methanoanthracen-11-ol (2).—To a mixture of 4.56 g of magnesium turnings and 5 g of indene in 140 ml of tetrahydrofuran in a nitrogen atmosphere was added a solution of 30.2 g of *o*-bromofluorobenzene in 90 ml of tetrahydrofuran. After refluxing for 3 hr, the reaction mixture was hydrolyzed by the cautious addition of 50 ml of water. The precipitated inorganic salts were filtered, and the filtrate was dried over magnesium sulfate and evaporated. Vacuum distillation of the residue yielded three fractions. Fractions one (bp 100–115° (0.15 mm)) and two (bp 120–135° (0.15 mm)) which contained some solid material were combined (2.5 g) and a 100-mg sample was separated by thin layer chromatography on silica gel plates developed with hexane. The products were eluted with chloroform–methanol (1:1). A yield of 70 mg (22%) of the hydrocarbon **1** of R_f 0.65 was obtained as crystals. The mp 155–165° did not change on recrystallization from benzene–petroleum ether (30–60°): $\lambda_{max}^{CH_3OH}$, 271 mμ (ε 1770), and 278 mμ (ε 2280).

Anal. Calcd for $C_{15}H_{12}$: C, 93.71; H, 6.29. Found: C, 93.91; H, 6.21.

The crystalline fraction of R_f 0.0 consisted of 32 mg (9%) of the alcohol **2**. After recrystallization from methanol it melted at 184–185°: λ_{max}^{MeOH}, 213 mμ (ε 67,500), 270 (2960), and 277 (3820). The infrared spectrum was identical with that of a sample obtained from Professor Meinwald[6] and a mixture melting point was not depressed.

Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.35; H, 5.89.

The third distillation fraction (bp 160–200° (0.15 mm)) crystallized when triturated with petroleum ether. After recrystallization from benzene–petroleum ether it melted at 196–198°. Its melting point and ultraviolet spectrum are identical with that of triphenylene.

Anal. Calcd for $C_{18}H_{12}$: C, 94.70; H, 5.30. Found: C, 94.68; H, 5.08.

Registry No.—Benzyne, 462-80-6; indene, 95-13-6; **1**, 4448-88-8; **2**, 15924-27-3; triphenylene, 217-59-4.

Acknowledgment.—We wish to acknowledge a helpful discussion with Professor E. Wenkert and to thank Drs. E. Sehlittler and G. deStevens for support.

(11) G. Wittig and W. Merkle, *ibid.*, **75**, 1491 (1942).
(12) G. Wittig and E. Knauss, *Chem. Ber.*, **91**, 895 (1958).
(13) J. A. Berson and G. B. Aspelin, *Tetrahedron*, **20**, 2697 (1964).
(14) W. R. Roth, *Tetrahedron Lett.*, 1009 (1964).
(15) Nmr spectra were recorded on a Varian A-60 instrument for deuteriochloroform solutions using tetramethylsilane as an internal standard. Melting points were determined with a Thomas–Hoover apparatus.

A Convenient General Synthesis of Amidines

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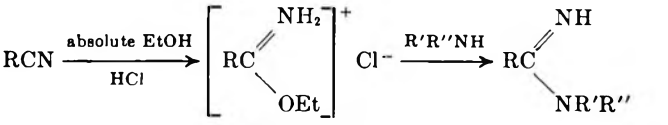
Received October 24, 1967

The most widely used procedure for the synthesis of amidines is the one described by Pinner at the end of the last century.[1] This method involves the preparation of an imidate salt by reaction of a nitrile and an anhydrous alcohol in the presence of an acid catalyst, usually hydrogen chloride. The imidate salt is then converted into the amidine by treatment with ammonia or an amine in absolute ethanol. Many amidines have been synthesized in excellent yield by the Pinner procedure, however, like most general methods, it has several limitations,[2] principally connected with the preparation of the imidate salts.[3] Perhaps its greatest shortcoming is that the starting nitriles are not readily available. In addition, the method has had no general application to the synthesis of *ortho*-substituted benzamidines because the necessary imidates are not formed or are obtained in very poor yield. Thus, only poor yields of *o*-chlorobenzamidine[2b] and 1-naphthamidine[2b] have been obtained and *o*-toluamidine has not yet been prepared despite several reported attempts.[2] Also, N,N′-disubstituted amidines cannot be synthesized by the Pinner procedure.



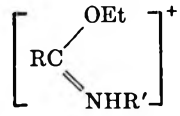
Pinner method

Amides are potentially more convenient starting materials. N-Substituted and N,N-disubstituted amidines may be prepared through intermediate imidoyl chlorides obtained by reacting secondary and tertiary amides with PCl_5, $POCl_3$, $SOCl_2$, and $COCl_2$.[2] However, these reagents dehydrate primary amides, making the procedure useless for unsubstituted amidines.

The O-alkylation of amides to produce imidate salts has been achieved with ethyl chloroformate,[4] dimethyl sulfate,[5] and triethyloxonium fluoroborate.[6] This procedure, involving electrophilic attack on the amide oxygen rather than nucleophilic attack on a sterically hindered nitrile carbon, should be superior for the preparation of *ortho*-substituted benzimidates. Bühner prepared methyl benzimidate methosulfate in good yield from benzamide and dimethyl sulfate, but he obtained only an unspecified yield of a heavy oil with N-methylbenzamide.[5] Bredereck and coworkers[7] have synthesized N,N,N′-trisubstituted and N,N,N′,N′-tetrasubstituted formamidines and acetamidines by reacting amines with the oily adducts formed from dimethyl sulfate and the appropriate secondary or tertiary formamides and acetamides. Other workers have treated the free imidate bases with amines and amino acids to prepare amidines and amidinelike compounds.[5,8] Aside from the work of Bredereck, *et al.*, there have been no reports of

(1) A. Pinner, "Die Imidoather und ihre Derivate," R. Oppenheim, Berlin, 1892.
(2) (a) For a relatively recent review of amidine synthesis, see H. Soll in Houblen-Weyl's, "Methoden der organischen Chemie," 4th ed, Vol. XI, Part 2, VEB Georg Thieme Verlag, Stuttgart, 1958, p 39. (b) For other discussions see P. Oxley and W. F. Short, *J. Chem. Soc.*, 147 (1946); F. C. Schaefer and A. P. Krapcho, *J. Org. Chem.*, **27**, 1255 (1962), and references cited therein.
(3) The chemistry of imidates has been reviewed by R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).
(4) W. Hechelhammer, German Patent 948,973 (1956).
(5) A. Bühner, *Ann.*, **333**, 289 (1904).
(6) H. Meerwein, E. Battenberg, H. Gold, E. Pfeil, and G. Willfang, *J. Prakt. Chem.*, **154**, 83 (1939).
(7) See H. Bredereck, F. Effenberger, and E. Henseleit, *Ber.*, **98**, 2754 (1965), and earlier papers cited therein.
(8) S. Petersen and E. Tietze, *Ann.*, **623**, 166 (1959)

TABLE I

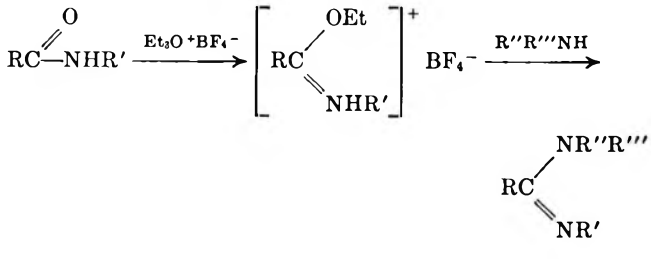


R	R′	Yield, %	Mp, °C	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
C_6H_5	H	80.6[a]	130–131	45.60	5.11	5.91	46.23	5.41	5.82
o-$CH_3C_6H_5$	H	80.1	93–94	47.84	5.62	5.58	47.89	5.56	5.58
1-Naphthyl	H	97	88–89	54.31	4.91	4.88	53.06	5.34	4.92
o-$C_2H_5OC_6H_5$	H	90[b]	139–141	47.00	5.74	4.98	47.44	5.57	4.85
o-ClC_6H_5	H	78	101.5–103	39.82	4.08	5.16	39.65	4.22	5.15
CH_3	H	[c]							
C_6H_5	CH_3	90.1	73–74	47.84	5.62	5.58	47.48	5.49	5.56

[a] Most of the product precipitated from the CH_2Cl_2 solution during the reaction. [b] The starting o-ethoxybenzamide was soluble in CH_2Cl_2. [c] The crude imidate was converted into the amidine without isolation. Triethyloxonium fluoroborate was added to acetamide below 5° and the mixture was allowed to warm to room temperature overnight. The solvent was removed completely *in vacuo* and the residue was treated with absolute alcoholic ammonia.

the direct utilization of imidate methosulfates or fluoroborates for the synthesis of amidines.

We report here that these imidate salts can readily be converted into amidines. We find that triethyloxonium fluoroborate[9] is distinctly superior to dimethyl sulfate for the O-alkylation of amides. For this reason we report in the Experimental Section only on the preparation of imidate fluoroborates and their conversion into amidines. Yields are excellent in both steps with triethyloxonium fluoroborate. By comparison, yields of the imidate methosulfates and amidines were good with benzamide and o-toluamide and fair with o-chlorobenzamide (56% yield of o-chlorobenzimidate methosulfate and 71% yield of amidine). With N-methylbenzamide we, like Bühner,[5] were unable to obtain a crystalline imidate methosulfate and isolated only an oil with a maximum possible yield of 23%. When N,N′-dimethylbenzamidine hydrochloride was prepared without isolation of the imidate methosulfate,[10] the over-all yield was 15% as compared to 90% yields in each step with triethyloxonium fluoroborate. In view of these results, triethyloxonium fluoroborate is the preferred reagent for the preparation of the imidate salt.



The imidate fluoroborates are crystalline solids which are decomposed by moisture, but are considerably more stable than triethyloxonium fluoroborate. KBr pellets of these salts exhibit a characteristic strong broad absorption from 1020 to 1120 cm^{-1} which is due to BF_4^-[11] and a sharp peak in the region of 1600–1700 cm^{-1} due to C=N stretching.[12]

(9) For a description of current procedures for preparation and storage of triethyloxonium fluoroborate, see H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

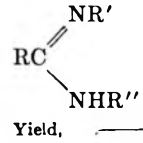
(10) See ref *c* in Table I.

(11) N. B. Colthup, L. H. Daly, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press Inc., New York, N. Y., 1964, p 361.

(12) Reference 11, p 283.

In the Experimental Section we describe general procedures for the preparation of the imidate fluoroborates and the amidines. No attempt has been made to optimize the conditions. The imidates and amidines are listed in Tables I and II, respectively, and variations of individual preparations from the general procedures are described in the footnotes to the tables.

TABLE II



R	R′	R″	Yield, %	Mp, °C Base	Mp, °C HCl	Mp, °C Picrate
C_6H_5	H	H	71.5[a]		166–168[b]	
o-$CH_3C_6H_5$	H	H	90[c]	104–105[d,e]	258–258.5[f]	235–236[g]
1-Naphthyl	H	H	75[c]	153–154.5[b,h]		226.5[b]
o-$C_2H_5OC_6H_5$	H	H	91[a]		195–196[j,k]	213–215[l]
o-ClC_6H_5	H	H	90[a]		280–282[m]	218–220[n]
CH_3	H	H	78[p]			249–251[b]
C_6H_5	CH_3	CH_3	90[c]		255–256[b]	171–172[b]

[a] Calculated as the hydrochloride. [b] Value agrees with literature. [c] Calcd as the free base. [d] Purified by sublimation at 80° (0.5 mm). [e] Calcd for $C_8H_{10}N_2$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.58; H, 7.50; N, 20.81. [f] Calcd for $C_8H_{11}N_2Cl$: C, 56.31; H, 6.50; N, 16.42. Found: C, 56.51; H, 6.48; N, 16.54. [g] Calcd for $C_{14}H_{13}N_5O_7$: C, 46.28; H, 3.61; N, 19.28. Found: C, 46.43; H, 3.70; N, 19.37. [h] Sublimed at 130° (0.5 mm). [i] Melting point reported by A. Pinner [*Ber.*, **23**, 2942 (1890)] is 218°. [k] Calcd for $C_9H_{13}ClN_2O$: C, 53.87; H, 6.53; N, 13.96. Found: C, 54.15; H, 6.82; N, 13.47. [l] Calcd for $C_{15}H_{15}N_5O_8$: C, 45.81; H, 3.84; N, 17.80. Found: C, 45.84; H, 4.05; N, 17.75. [m] Calcd for $C_7H_8N_2Cl_2$: C, 44.01; H, 4.22; N, 14.66. Found: C, 44.13; H, 4.35; N, 14.63. [n] Calcd for $C_{13}H_{10}N_6O_7Cl$: C, 40.69; H, 2.63; N, 18.25. Found: C, 41.21; H, 2.78; N, 18.21. [p] Over-all yield of amidine picrate based on acetamide.

Experimental Section

A solution of 0.1 mol of triethyloxonium fluoroborate in 50 ml of dry CH_2Cl_2 (reagent grade distilled from anhydrous $CaCl_2$) was added over 5 min at room temperature to a suspension of 0.1 mol of the amide in 200 ml of dry CH_2Cl_2. The mixture was stirred overnight at room temperature during which time a clear solution resulted. The solution was evaporated *in vacuo* to one-third volume and treated with five volumes of anhydrous ether. The precipitated imidate fluoroborate was filtered and dried *in vacuo*. The salts could be recrystallized for analysis from dichloromethane or dichloromethane–ether. The crude salts were used in all cases for the amidine preparation.

The amidines were prepared by the procedure described by Dox.[13] The imidate fluoroborate was stirred at room tempera-

(13) A. W. Dox, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1951, p 5.

ture in a tightly stoppered flask with an 8–9% solution of ammonia or methylamine in absolute ethanol containing approximately a 40% excess of amine. After 3 days the mixture was evaporated to dryness *in vacuo* and treated with a small volume of water. The mixture was made strongly basic with 5 *N* NaOH and the insoluble oil was extracted into ethyl acetate or ether. The oil which remained after evaporation *in vacuo* of the organic solvent was either crystallized and purified or converted into the hydrochloride. A portion was also converted into the picrate.

Stereospecific Vinyl Halide Substitution. III. *cis*- and *trans*-Vinylenebis(diphenylarsines) and Their Rhodium Complexes

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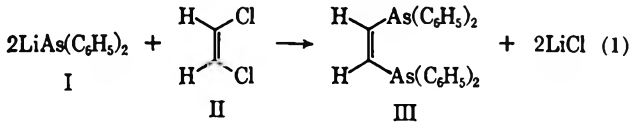
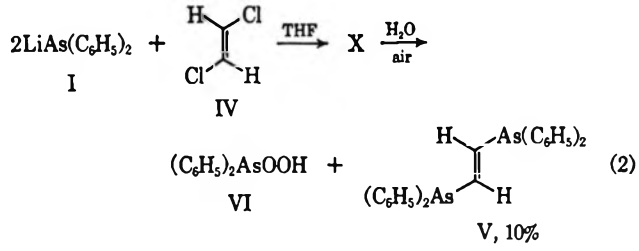
During a study of vinylarsines we reported the stereospecific replacement of the vinyl bromides in the β-bromostyrenes by lithium diphenylarsenide (I).[2] This replacement occurred with retention of configuration.

We wish to report that lithium diphenylarsenide (I) (prepared from triphenylarsine and lithium)[2] reacts with *cis*-1,2-dichloroethene (II), in tetrahydrofuran solution, to give *cis*-vinylenebis(diphenylarsine) (III) in 61% yield (eq 1).



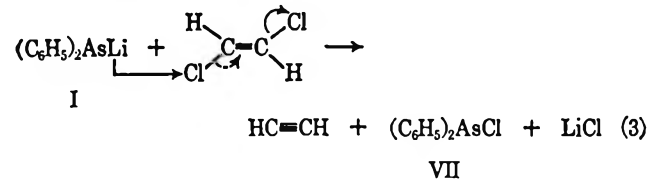
Treatment of I with *trans*-1,2-dichloroethene (IV) under the same conditions produced only 10% of *trans*-vinylenebis(diphenylarsine) (V). The major product isolated was diphenylarsinic acid (VI) (eq 2).



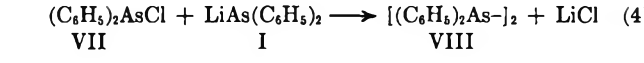
This is in contrast to the reaction of lithium diphenylphosphide with *cis*- and *trans*-1,2-dichloroethene which leads to *cis*- and *trans*-vinylenebis(diphenylphosphine), respectively, both in excellent yields.[3] Changing the order of addition of reactants did not greatly alter the yields of V and VI.

No *trans*-diarsine (V) was obtained from the reaction of *cis* dichloride (II), and no *cis*-diarsine (III) was obtained from the *trans* dichloride (IV). Therefore an elimination–addition sequence can be excluded since a common intermediate such as acetylene or chloroacetylene would lead to the same product(s) from both isomeric dichlorides. Evidence has been obtained supporting the idea that *trans*-diarsine (V) is stable under the conditions employed. This has been shown by vpc analysis on a 3% SE-30 column at 250° using a flame ionization detector.

It seems that a reaction path lower in activation energy than the halide replacement and leading to diphenylarsenic acid (VI) (or precursor) is possible in the reaction of I with IV. A possible explanation could be halogen–metal interchange, which seems to occur more readily with lithium arsenides than with lithium phosphides. This would be favored with IV (over II) due to the *trans* coplanarity of the halogens in IV and consequent ease of elimination (eq 3).



Depending on the order of addition of reagents, chlorodiphenylarsine (VII) may or may not react with excess I to give tetraphenyldiarsine (VIII) (eq 4).



Both VII and VIII will react with water and air to produce VI and work is now in progress in an attempt to elucidate the actual pathway by which VI is produced.

An elimination–addition sequence would involve a common intermediate (chloroacetylene) for both the *cis*- and *trans*-dichloroethenes and therefore both reactions would be expected to produce the same or a mixture of isomers. In fact, however, gas chromatographic analysis of the crude reaction mixtures shows that only *one* diarsine is produced from the *cis*-dichloroethene and that it has a distinctly different retention time from the *one* diarsine produced from the *trans*-dichloroethene. Thus the two reactions give different, single products with no mixtures of the two diarsines being found in the same reaction mixture.

Support for the structure assignments III and V as the *cis* and *trans* isomers, respectively, comes from elemental analysis, infrared and proton nmr spectra, and dipole moment measurements. These moments are given in Table I along with those of *cis*- and *trans*-vinylenebis(diphenylphosphine) whose structures have previously been established.[3] From these data, it is clear that the structure assignments made above are the correct ones.

TABLE I

DIPOLE MOMENTS OF *cis*- AND *trans*-$((C_6H_5)_2M—CH=CH—M(C_6H_5)_2)$

Isomer	M = P	M = As
cis	1.96 D ± 0.21	1.37 D ± 0.09
trans	0.99 D ± 0.09	0.97 D ± 0.09

Further support for these structure assignments comes from the differing behavior of III and V when allowed to react with rhodium dicarbonyl chloride dimer (IX). The reaction of III produces an orange

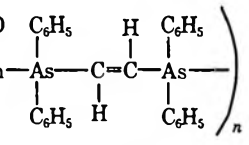
(1) (a) NASA Predoctoral Fellow, 1964–1967; (b) NDEA Predoctoral Fellow, 1966–1968.

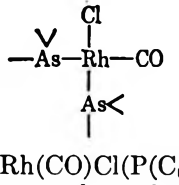
(2) A. M. Aguiar and T. G. Archibald, *J. Org. Chem.*, **32**, 2627 (1967).

(3) A. M. Aguiar and D. J. Daigle, *J. Amer. Chem. Soc.*, **86**, 2299 (1964).

monomeric complex (X) containing two diarsine moieties and no carbonyl groups which can be readily isolated as the tetrafluoroborate salt from methanol. The complex has an equivalent conductivity of 79.7 ohm^{-1} cm^{-1} in nitromethane solution (10^{-3} M) and is thus a 1:1 electrolyte (typical conductivities for *ca.* 10^{-3} *M* solutions of 1:1 electrolytes in nitromethane are in the range 80–100 ohm^{-1} cm^{-1}).[4-6] It thus appears to be strictly analagous to those complexes formed from IX and ethylenebis(diphenylphosphine)[7] and *cis*-vinylenebis(diphenylphosphine).[3,8] We therefore also formulate X as a square planar complex of Rh(I) containing chelating ligands. This could only be possible if the ligand in the complex were in the *cis* configuration. There is, of course, the possibility that III is a *trans* isomer that has isomerized upon reaction with IX as has been found to occur when the analogous *trans*-vinylenebis(dimethylarsine) is treated with Pd(II).[9] However, we feel that this is quite unlikely since the dipole moment data show that III is undoubtedly the *cis* isomer at the beginning. (See also below.)

By contrast, treatment of V with IX produces a very insoluble yellow complex (XI) containing only *one* diarsine moiety per rhodium. The presence of a strong band in the infrared at 5.04 μ shows that there is still one terminal carbonyl group present. Such behavior is characteristic of the reactions of nonchelating arsines and phosphines with IX, the usual product being *trans*-$Rh(CO)ClL_2$ (L = phosphine or arsine).[10] Thus the production of a carbonyl-containing species strongly suggests that V is not capable of chelating and is therefore most probably the *trans*-diarsine. Since it is bifunctional, it would be expected that both ends would coordinate which would lead to a polymeric complex. This is supported by the extreme insolubility of XI. Furthermore, an analogous complex is formed from IX and the known *trans*-vinylenebis(diphenylphosphine)[3,8] thereby strongly suggesting that V is also a *trans* isomer. The infrared spectrum of (XI) shows, in addition to the strong band at 5.04, a weak shoulder at *ca.* 5.00 μ. We suggest that this is due to a small proportion of *cis* attachment of the diarsine to rhodium in the polymer *viz.*





The complex *cis*-$Rh(CO)Cl(P(C_6H_5)_3)_2$ has recently been reported and it was shown here that the position of the carbonyl band was about 0.05 μ lower than for the *trans* isomer.[11]

When V is treated with IX in methanol in the presence of tetrafluoroborate ion, only the insoluble yellow complex XI is formed and no BF_4^- is incorporated into the complex. Thus under the conditions employed V does not isomerize to a species capable of chelating and hence we conclude that III, which produces a chelate complex, must be the *cis* isomer.

Experimental Section

All reactions involving lithium diphenylarsenide were carried out in dry apparatus under nitrogen. Tetrahydrofuran was dried over calcium hydride and filtered before use. All other chemicals were reagent grade and were used as received. Infrared spectra were obtained on Beckmann IR-5A and IR-8 instruments on potassium bromide pellets and Nujol mulls. Proton nmr spectra were obtained on a Varian A-60 instrument using deuteriochloroform as a solvent and tetramethylsilane as an internal standard. The gas chromatographic studies utilized a Micro-Tek instrument with a 3% SE-30 column and flame-ionization detector. Conductivity measurements were made using a Thomas-Serfass Model RCM15B1 conductivity bridge, and dipole moment measurements were determined on a General Radio 1615-A capacitance bridge, a Balsbaugh 2TN50 cell, and a Bausch and Lomb Modified Abbe-type refractometer on 10^{-3} *M* benzene solutions. Microanalyses were by Galbraith Laboratories, Knoxville, Tenn. All melting points are uncorrected.

Reaction of *cis*-1,2-Dichloroethene.—In a dry apparatus, under nitrogen, was placed 1.2 g (0.0125 mol) of *cis*-1,2-dichloroethene in 40 ml of tetrahydrofuran (THF). A THF solution of lithium diphenylarsenide[2] (25 ml, 0.025 mol) was added slowly. The reaction was very exothermic and immediate decolorization of the arsenide solution occurred upon contact with the halide. When the addition was complete, the slightly yellow solution was allowed to cool. Water (1 ml) was added and an exothermic reaction occurred with complete decolorization of the solution. This hydrolyzed solution was allowed to stand 5 min and the solvent was removed on a rotary evaporator. The resulting oil was extracted with basic water and a solid formed. Filtration and recrystallization from ethanol gave 3.7 g (61%) of *cis*-vinylenebis(diphenylarsine) (III), mp 112–113.

Anal. Calcd for $C_{26}H_{22}As_2$: C, 64.49; H, 4.55; As, 30.95. Found: C, 64.78; H, 4.62; As, 30.60.

Infrared absorptions (KBr) appeared at 3.3 (w), 6.45 (w), 6.8 (m), 7.0 (m), 7.7 (w), 7.9 (m), 8.45 (w), 8.65 (w), 9.3 (m), 9.4 (m), 9.8 (m), 10.0 (m), 11.05 (w), 13.7 (s), and 14.5 (s) μ.

The 60-MHz proton nmr spectrum of the *cis*-vinylenebis(diphenylarsine) (III) in deuteriochloroform solution showed a phenyl proton signal centered at τ 2.7 and a vinyl proton singlet at 2.55. The relative ratios were 10:1, respectively.

Reaction of *trans*-1,2-Dichloroethene.—To 50 ml of a THF solution of 1.2 g of *trans*-1,2-dichloroethene (0.0125 mol) was added slowly 25 ml of THF solution of the lithium diphenylarsenide (0.025 mol). The reaction was very exothermic and decolorization of the arsenide solution occurred. The solvent was stripped off and the resulting oil was extracted with aqueous base (5% KOH solution). The oil turned into a semisolid, and the water was decanted. Trituration of the semisolid with an ethanol–acetone mixture (6:1) gave a solid which was filtered off. Recrystallization from ethanol gave a 10% yield of *trans*-vinylenebis(diphenylarsine) (V), mp 103–104.

Anal. Calcd for $C_{26}H_{22}As_2$: C, 64.49; H, 4.55; As, 30.95. Found: C, 64.45; H, 4.65; As, 30.97.

Infrared bands (KBr) were at 3.3 (w), 6.3 (w), 6.8 (m), 7.0 (m), 7.7 (w), 7.95 (w), 8.45 (w), 8.8 (m), 9.3 (m), 9.4 (m), 9.8 (m), 10.0 (m), 10.2 (m), 11.05 (w), 13.7 (s), and 14.5 (s) μ.

The 60-MHz proton nmr spectrum of a deuteriochloroform solution of V showed a phenyl proton signal at τ 2.6, and a vinyl proton singlet at 2.9, with a relative ratio of 10:1.

This compound showed a depressed, mixture melting point with the compound prepared from *cis*-1,2-dichloroethene.

(4) C. M. Harris and T. N. Lockyer, *J. Chem. Soc.*, 3083 (1959).
(5) N. S. Gill and R. S. Nyholm, *ibid.*, 3997 (1959).
(6) J. E. Fergusson and R. S. Nyholm, International Conference on Coordination Chemistry, London, April 1959, No. 62.
(7) A. Sacco and R. Ugo, *J. Chem. Soc.*, 3274 (1964).
(8) J. T. Mague, Department of Chemistry, Tulane University, unpublished results.
(9) M. A. Bennett, G. J. Erskine, and J. Wild, unpublished work quoted by W. R. Cullen, P. S. Dahliwal, and C. J. Stewart, *Inorg. Chem.*, **6**, 2256 (1967).
(10) L. Vallarino, *J. Chem. Soc.*, 2287 (1957).
(11) T. Blum, E. Oppenheimer, and E. O. Bergmann, *J. Amer. Chem. Soc.*, **89**, 2338 (1967).

Diphenylarsenic acid was obtained in 60% yield by acidification of the alkaline water solution. Infrared and nmr spectra as well as melting point and mixture melting point determinations with an authentic sample were used to establish the identity of this product.

Bis(*cis*-vinylenebis(diphenylarsine))rhodium(I) Tetrafluoroborate Methanol Solvate.—To 0.1 g (0.26 mmol) of $[Rh(CO)_2Cl]_2$ in 15 ml of anhydrous methanol under nitrogen was added 0.5 g (1.04 mmol) of *cis*-$(C_6H_5)_2AsCH{=}CHAs(C_6H_5)_2$ in 10 ml of anhydrous methanol. The yellow orange solution darkened immediately and carbon monoxide was evolved. The solution was refluxed for 5 min and a stoichiometric amount of $NaBF_4$ was added. Upon adding *ca.* 15 ml of diethyl ether and cooling, bright orange crystals of X (0.4 g, 80%) formed. These were filtered off, washed with ether, and dried *in vacuo*, mp 238 dec.

Anal. Calcd for $C_{62}H_{44}As_4RhBF_4 \cdot CH_3OH$: C, 53.47; H, 4.09; As, 25.17; F, 6.38. Found: C, 52.72; H, 4.09; As, 25.74; F, 5.94.

The infrared spectrum (Nujol mull) showed bands due to the diarsine, the BF_4^- ion, and a sharp band of medium intensity at 2.84 μ which can be assigned to the O–H stretching frequency of methanol. No band in the region 4.75–5.60 μ was observed indicating that all the carbonyl groups had been displaced.

Chlorocarbonyl(*trans*-vinylenebis(diphenylarsine))rhodium(I). Benzene solutions (*ca.* 10 ml each) of 0.1 g (0.26 mmol) of rhodium dicarbonyl chloride dimer and 0.25 g (0.52 mmol) of V were combined at room temperature under nitrogen. Immediate effervescence occurred as carbon monoxide was evolved and the yellow solution became orange. Slow addition of diethyl ether accompanied by mild agitation with a nitrogen stream caused the precipitation of pale yellow microcrystals of XI. These were filtered off, washed well with hot N,N-dimethylformamide, and dried *in vacuo*. The complex decomposes without melting at 235°.

Anal. Calcd for $C_{27}H_{22}As_2OClRh$: C, 49.83; H, 3.41; Cl, 5.45. Found: C, 49.91; H, 3.43; Cl, 5.97.

The infrared spectrum of XI in a Nujol mull showed, in addition to bands due to the diarsine, a strong band at 5.04 with a weak shoulder at 5.00 μ. In addition, the sharp "*trans*" band at 10.2 has shifted to 10.35 μ while becoming weaker and broader.

The complex is extremely insoluble in all common organic solvents thus rendering a molecular weight determination impossible.

Registry No.—III, 15924-20-6; V, 15924-21-7; X, 15956-79-3.

Acknowledgment.—Thanks are extended to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, and to the National Science Foundation for its contribution toward the cost of the instruments used. We also wish to acknowledge the help of Mr. George Linthicum and of Mr. Jonathan Bullock for obtaining the dipole moment data.

The Thermal Isomerization of Abietic Acid[1a]

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Received August 28, 1967

It has been reported from this laboratory that levopimaric acid,[2] neoabietic acid,[3] and palustric acid,[4] on heating, isomerize to give abietic acid. The reverse reaction, that is, the thermal isomerization of abietic acid to give levopimaric and palustric acids, has not been reported. The isolation of 1% of neoabietic acid from abietic acid which had been heated at 300° for 20 min was noted.[5] It was therefore decided to investigate the isomerization of abietic acid at an elevated temperature to determine its behavior in detail.

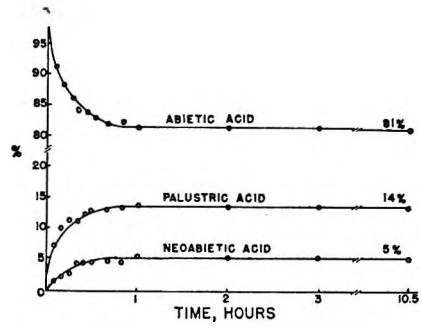

Figure 1.—The isomerization of abietic acid at 200°.

Samples of pure abietic acid were sealed in glass tubes under nitrogen and immersed in a 200° bath. Tubes were removed at intervals and the product analyzed by means of glpc,[6] optical rotation, and ultraviolet absorption spectra. Surprisingly, it was found that abietic acid undergoes a rapid isomerization to give a final equilibrium mixture of 81% abietic, 14% palustric, and 5% neoabietic acid (*cf.* Figure 1.)

Gas–liquid partition chromatography indicated only three peaks in the curve. These peaks were identified by means of relative retention times, infrared and ultraviolet absorption spectra, and optical rotation. The absence of any significant amount of levopimaric acid in the final 81%:14%:5% isomerization mixture was confirmed by the value of the optical rotation of the collected palustric and/or levopimaric peak.[6]

The isomerization of abietic acid was repeated at 180°. The reaction was found to follow first-order kinetics with respect to abietic acid for the first hour of the isomerization; $k = 3.7 \times 10^{-5}$ sec^{-1} at 180° ($t_{1/2}$ = 5.2 hr).

The isomerization at 200° of palustric, levopimaric, and neoabietic acids was then carried out for the first time to the point at which no further isomerization occurred. It was found that all four (including abietic acid) conjugated dienoic resin acids exhibit the same final distribution of the three resin acids, namely 81% abietic, 14% palustric, and 5% neoabietic acids. This confirms the fact that a true dynamic equilibrium is reached among these three acids at 200°.

The acid isomerization of levopimaric acid[7] and neoabietic acid[8] at room temperature in the presence of mineral acids has been described. The isomerization of the four conjugated dienoic resin acids was repeated in 0.5 *N* ethanolic hydrochloric acid. It was found that all four acids eventually reached the same final distribution of resin acids, namely 93% abietic acid, 4% palustric acid, and 3% neoabietic acid. This confirms

(1) (a) Presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 1967. (b) National Academy of Sciences, National Research Council Postdoctoral Fellow. (c) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) V. M. Loeblich, D. E. Baldwin, R. T. O'Connor, and R. V. Lawrence, *J. Amer. Chem. Soc.*, **77**, 6311 (1955).

(3) V. M. Loeblich and Ray V. Lawrence, *ibid.*, **79**, 1497 (1957).

(4) N. M. Joye, Jr., and Ray V. Lawrence, *J. Org. Chem.*, **26**, 1024 (1961).

(5) G. C. Harris and T. F. Sanderson, *J. Amer. Chem. Soc.*, **70**, 334 (1948).

(6) T. W. Brooks, G. S. Fisher, and N. M. Joye, Jr., *Anal. Chem.*, **37**, 1063 (1965).

(7) D. E. Baldwin, V. M. Loeblich, and R. V. Lawrence, *J. Amer. Chem. Soc.*, **78**, 2015 (1956).

(8) P. F. Ritchie and L. F. McBurney, *ibid.*, **72**, 1197 (1950).

the fact that a dynamic equilibrium is reached in this system involving abietic, palustric, and neoabietic acids. The isomerization at 200° probably involves catalysis by the carboxylic acid group. The difference in temperature (25 *vs.* 200°) and environment probably accounts for the difference in the composition of the final equilibrium mixtures. The palustric acid peak was again collected, and, based on the observed rotation, it would appear that not more than a trace of levopimaric acid is present in the final equilibrium mixture. Previous workers[7] employing a partition chromatographic analytical method at room temperature reported values of 93% abietic, 4% palustric, and 2% neoabietic acids for the acid isomerization of abietic acid under the same conditions.

The acid-induced equilibria of the four conjugated dienoic resin acids probably involve a common carbonium ion.[8,9] The results of the isomerization experiments show an interesting difference in what might be expected in terms of thermodynamic stabilities.

It is interesting to note that the half-lives of the four conjugated dienoic resin acids at 200° correlate with the absorptivity of the resin acids ($t_{1/2}$, min; absorption at λ_{max}, mμ: levopimaric acid, 15, 19; palustric 40, 31; abietic 75, 77; neoabietic 120, 80). It is generally held that the absorptivity of the resin acids is related to ring strain.

It is of further interest to note that in the case of palustric acid, protonation must occur from the α side exclusively at C-9 or else a 9-β-H abietic and neoabietic acid would be formed. No appreciable amounts of any unknown peaks were observed in the glpc analyses.

Experimental Section

All optical rotations were determined in 95% ethanol at c 1.

Thermal Reactions.—About 0.2 g of each acid was placed in a glass Carius tube. The air in each tube was replaced with nitrogen. The tubes were then sealed under vacuum, submerged in an oil bath, and heated at 200°.

Isomerization of Abietic Acid at 200°.—The change in acid composition with time is plotted in Figure 1. Only three peaks were observed in the glpc analysis through 10.5 hr (no disproportionation observed). These were identified as methyl abietate, palustrate, and neoabietate by means of relative retention times, infrared and ultraviolet absorption spectra, and optical rotation. The value for the methyl palustrate peak was $[\alpha]^{25}D$ +65.2 (theory +68.4).

Isomerization of Abietic Acid in the Presence of Potassium Hydroxide at 200°.—Abietic acid was dissolved in methanol containing potassium hydroxide (1:0.05 mole ratio). The solvent was removed under vacuum. The residual solid was heated at 200° in the usual manner. The system reached the equilibrium distribution in about 8 hr.

Isomerization of Palustric, Levopimaric, and Neoabietic Acids at 200°.—A final equilibrium distribution of 81% abietic, 14% palustric, and 5% neoabietic acid was obtained in all cases. Essentially no disproportionation was observed at the end of 21.5 hr in the case of neoabietic and levopimaric acids. A total of 6.1% of resin acids other than abietic, palustric, and neoabietic acids were observed to be present at the end of 24 hr in the case of palustric acid.

Acid Isomerization of Abietic, Levopimaric, Palustric, and Neoabietic Acids.—A 1% solution of each of the four conjugated dienoic resin acids was made in a 0.5 *N* ethanolic solution of hydrochloric acid. Aliquots were removed periodically and poured into water. The resin acids were immediately extracted with ether, the ether was stripped off (quantitative yield), and the residue was analyzed. The methyl palustrate peak exhibited $[\alpha]^{25}D$ +67.7° (theory for methyl palustrate is $[\alpha]^{25}D$ +68.4°). The final equilibrium distribution for all four acids (50 hr at room temperature) was 93% abietic, 4% palustric, and 3% neoabietic acids. No disproportionation was observed in any of the four acids.

Registry No.—Abietic acid, 514-10-3.

(9) W. H. Schuller, R. N. Moore, and R. V. Lawrence, *J. Amer. Chem. Soc.*, **82**, 1734 (1960).

Oxidation of 3β-Acetoxy-14α-methyl-5α-cholest-7-ene[1]

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The susceptibility of 3β-acetoxy-14α-methyl-5α-cholest-7-ene (I) to oxidation by chromium trioxide has already been noted, and this property was used as a means of removing olefin I from a reaction mixture.[2] At the time oxidation was performed on a microscale, and the products were not further investigated. Recently, it became necessary to review the reaction in more detail, and one of the products has now been found to arise by an unusual allylic oxidation.

Small-scale studies showed that oxidation (room temperature) of olefin I with chromium trioxide in aqueous acetic acid was essentially complete in 1 hr. When the reaction was carried out on a larger scale, thin layer chromatography (tlc) of the crude product showed three main spots. Preparative tlc (on silica) led to three crystalline products, each of which was subjected to further purification by the same technique. The main product was the expected 7,11-dione II.[3] A thin band close to the leading edge of the diketone (II) zone provided saturated ketone III,[4] and a third zone gave a new compound which showed an infrared band at 1670 cm^{-1}, typical of an α,β-unsaturated ketone. The latter substance was not Δ^8-7-ketone IV as anticipated. This possibility was eliminated by comparison with an authentic sample, synthesized by Jones oxidation of 8α,9α-epoxy 7α-alcohol Va to ketone Vb followed by treatment with zinc in acetic acid.[5]

A rotatory dispersion curve of the new ketone exhibited a positive Cotton effect in methanol, and in petroleum ether solution showed all the fine structure associated with a Δ^7-6-keto system[6] (Figure 1). The ultraviolet absorption curve showed a maximum at 245

(1) (a) Steroids and Related Natural Products. XLV. For part XLIV, see T. R. Kasturi, G. R. Pettit, and K.A. Jaeggi, *Chem. Commun.*, 644 (1967). (b) The present contribution was supported by Public Health Service Research Grant 1 RO1 CA-10115-01 from the National Cancer Institute and by National Science Foundation Grant No. GB-4939.

(2) J. C. Knight, P. D. Klein, and P. A. Szczepanik, *J. Biol. Chem.*, **241**, 1502 (1966).

(3) (a) R. B. Woodward, D. A. R. Barton, A. A. Patchett, D. A. H. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957); and (b) J. C. Knight, C. Djerassi, and D. I. Wilkinson, *J. Amer. Chem. Soc.*, **88**, 790 (1966).

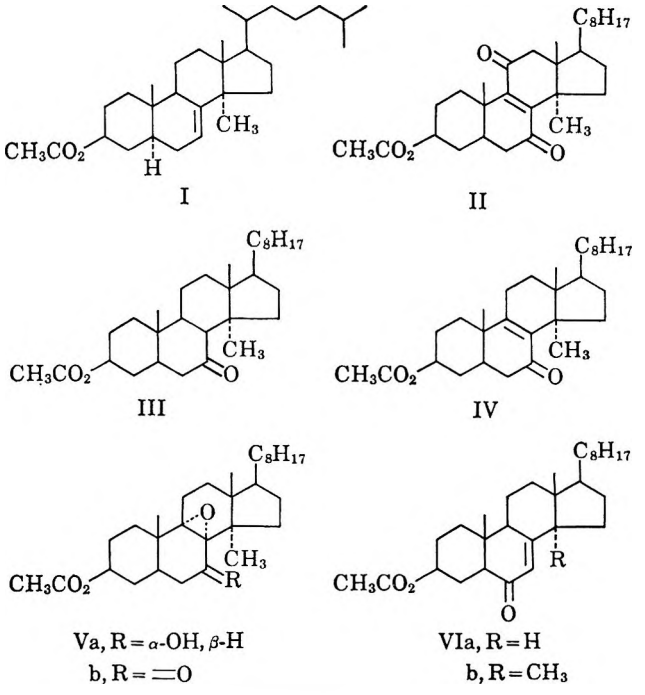
(4) J. C. Knight, J. Belletire, and G. R. Pettit, *J. Chem. Soc., Sect. C*, 2427 (1967).

(5) (a) L. F. Fieser, K. Nakanishi, and W. Y. Huang, *J. Amer. Chem. Soc.*, **75**, 4719 (1953); (b) L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 4395 (1953).

(6) C. Djerassi, J. C. Knight, and H. Brockmann, Jr., *Ber.*, **97**, 3118 (1964). This paper reports isolation of desoxyviperidone from the cactus *Wilcoxia viperina*. The following spectral data are given for 3β-acetate VIa: λ_{max} 245 mμ (ε 13,500); ν_{max} 1665 cm^{-1}; nmr, δ 0.63 (18-Me), 0.87 (19-Me), 5.71 (7-H). Effect of the 14α-methyl group on the 18- and 19-methyl nmr signals is briefly discussed in ref 3b.

mμ (ε 13,920), and the nmr spectrum exhibited a signal at 5.78 due to the α proton of an α,β-unsaturated ketone system. These data corresponded closely with those determined for a sample of the acetate of deoxyviperidone (VIa).[6,7] Accordingly, the new ketone was formulated as 3β-acetoxy-6-oxo-14α-methyl-5α-cholest-7-ene VIb.[8]

Chromium trioxide oxidation of Δ^7 sterols and triterpenoids has not previously been reported to yield a 6-ketone,[9] presumably because sterols suffer preferential attack at the 14 hydrogen (blocked in this case by a methyl group), and the presence of a triterpenoid 4,4-



dimethyl group results in increased steric hindrance at C-6. However, such allylic oxidations may be more general in scope, and before the advent of preparative tlc may have escaped detection.

Experimental Section[10]

Chromium Trioxide Oxidation of 3β-Acetoxy-14α-methyl-5α-cholest-7-ene (I).—A solution of chromium trioxide (1.0 g) in acetic acid (40 ml) containing just enough water to ensure a clear solution was added to a solution of 3β-acetoxy-14α-methyl-5α-cholest-7-ene (I, 1.0 g) in glacial acetic acid (60 ml). The mixture was allowed to stand at room temperature for 90 min (tlc showed no starting material remaining). Following dilution with water and extraction with diethyl ether, the extract was washed well with water, aqueous sodium hydrogen carbonate, and water, dried, and concentrated. The residual yellow oil was separated into three zones on four chromatoplates developed three times in ethyl acetate–ligroin (15:85). Each of the three zones was further purified in the same manner, then recrystallized from methanol to give, in order of increasing polarity, (1) 3β-acetoxy-7-oxo-14α-methyl-5α-cholestane (III) crystallizing in colorless needles [155 mg; mp 118–120° (ketone III did not depress the melting point of an authentic sample[4] prepared by peracid oxidation of olefin I, and their infrared spectra were identical)], (2) 3β-acetoxy-7,11-dioxo-14α-methyl-5α-cholest-8-ene (II) obtained as yellow needles [390 mg; mp 113–115°; λ_{max} 271 mμ (ε 8253); ν_{max} 1740, 1680 cm^{-1} (lit.[3b] mp 116–118°); λ_{max} 271 (ε 8404); ν_{max} 1739, 1681 cm^{-1})], and (3) 3β-acetoxy-6-oxo-14α-methyl-5α-cholest-7-ene (VIb) crystallizing in small colorless prisms [80 mg; mp 170–172°; nmr, 0.72 (18-Me), 0.84 (19-Me), 0.90, 0.94, 1.12, 2.06 (acetate), 4.75 (3-H), 5.78 (7-H); $[\alpha]_D$ 0°; ORD (in methanol, *c* 0.037), $[\alpha]_{650}$ +163, $[\alpha]_{500}$ +217°, $[\alpha]_{460}$ +217°, $[\alpha]_{400}$ +272°, $[\alpha]_{345}$ +1140° (peak), $[\alpha]_{326}$ 0°, $[\alpha]_{290}$ −3153 (inflexion); λ_{max} 245 mμ (ε 13,920); ν_{max} 1670, 1615, 1735, 1240 cm^{-1}].

Anal. Calcd for $C_{30}H_{48}O_3$ (456): C, 78.89; H, 10.59. Found: C, 78.76; H, 10.55; mol wt (mass spectroscopy), 456.

3β-Acetoxy-7-oxo-14α-methyl-5α-cholest-8-ene (IV).—A solution of 1.0 g of 3β-acetoxy-7α-hydroxy-8α,9α-epoxy-14α-methyl-5α-cholestane (Va was obtained as a by-product from oxidation of 3β-acetoxy-14α-methyl-5α-cholest-7-ene (I) with *m*-chloroperbenzoic acid in chloroform)[4] in acetone was treated (dropwise) with Jones reagent[11] until an orange tinge was present. The solution was diluted with water and extracted with diethyl ether; the extract was washed well with water and aqueous sodium hydrogen carbonate, dried, and concentrated. The residue was chromatographed (column) on silica gel (0.05–0.20 mm, E. Merck, Darmstadt). Elution with 19:1 ligroin–ethyl acetate gave ketone Vb as a homogeneous crystalline solid (0.8 g) which no longer showed hydroxyl absorption in the infrared spectrum, but exhibited a strong carbonyl band at 1700 cm^{-1}. Without further characterization, ketone Vb was dissolved in acetic acid (50 ml) and zinc dust (1.0 g) was added. The mixture was heated at reflux for 1 hr, cooled, filtered, and diluted with water. Extraction with diethyl ether provided (after washing and concentrating) a colorless oil which was purified by preparative layer chromatography on four plates developed in ethyl acetate–ligroin (1:4). The main zone provided 3β-acetoxy-7-oxo-

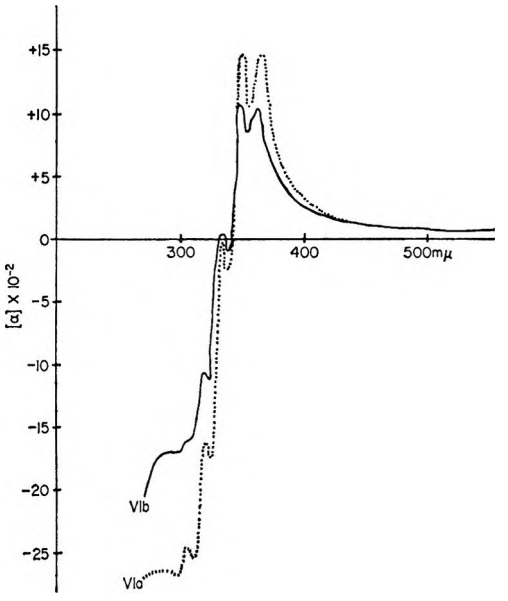


Figure 1.—Rotatory dispersion curves in ligroin solution: ———, 3β-acetoxy-6-oxo-14α-methyl-5α-cholest-7-ene (VIb); · · · ·, desoxyviperidone acetate (VIa) (3β-acetoxy-6-oxo-5α-cholest-7-ene) from *Peniocereus greggii*.[7]

(7) Isolated from the cactus *Peniocereus greggii*, J. C. Knight and G. R. Pettit, unpublished results.

(8) Preparation of ketone VIb affords, in principle, a route to naturally occurring 14α-methyl steroids of the Macdougallin (3β,6α-dihydroxy-14α-methyl-5α-cholest-8-ene) type (*cf.* ref 3b).

(9) For examples of the oxidation of the Δ^7-sterol and triterpene series, see ref 5a and b, and also C. Djerassi, G. W. Krakower, A. J. Lemin, L. H. Liu, J. S. Mills, and R. Villotti, *J. Amer. Chem. Soc.*, **80**, 6284 (1958), and references cited therein.

(10) All solvents were redistilled, and ligroin refers to a fraction boiling at 60–70°. Extracts of aqueous solutions were dried over anhydrous magnesium sulfate. Preparative thin layer chromatography was performed using silica gel HF_{254} (E. Merck, Darmstadt) in 2-mm layers on 200 × 200 mm plates. Melting points were observed using a Fisher-Johns apparatus and are uncorrected. The ultraviolet (methanol solution, Cary spectrophotometer), infrared (KBr disks, Beckman IR-12), and nuclear magnetic resonance spectra (deuteriochloroform solution with tetramethylsilane as internal standard, Varian A-60), and optical rotatory dispersion (JASCO ORD/UV-5) measurements were determined by Miss K. Reimer. We also wish to thank John Occolowitz for the mass spectra (Atlas CH-4 spectrometer). The microanalyses were provided by Dr. A. Bernhardt, Max Planck Institut, Mülheim, Germany, and optical rotations at the sodium D line (chlorform solution at 20°) were determined by Dr. P. Demoen, Janssen Pharmaceutica, Beerse, Belgium.

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

14α-methyl-5α-cholest-8-ene (IV) as a solid which crystallized from methanol as large flat needles (460 mg): mp 114–117°; λ_{max} 254 mμ, (ε 9417); ν_{max} 1745, 1660, 1583 cm^{-1}; nmr, δ 0.66 (18-Me), 0.80, 0.90, 1.18 (19-Me), 4.70; $[\alpha]_D$ +19.5° (*c* 1.30); ORD (*c* 0.06 in ligroin), $[\alpha]_{450}$ +32°, $[\alpha]_{400}$ +94°, $[\alpha]_{367}$ +160° (peak), $[\alpha]_{344}$ 0°, $[\alpha]_{300}$ −480°, $[\alpha]_{280}$ −897°, $[\alpha]_{260}$ −2180°.

Anal. Calcd for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 78.89; H, 10.62.

Registry No.—I, 5259-20-1; II, 5535-18-2; III, 14156-34-6; IV, 15963-76-5; VIb, 15963-75-4.

The Reaction of α,β-Unsaturated Nitriles with Concentrated Sulfuric Acid

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Ritter and coworkers[2] have shown that the reaction between nitriles and branched olefins or tertiary alcohols in the presence of concentrated sulfuric acid led to the formation of N-alkylamides. This reaction was further studied,[3-9] and the general view[3,9] is that the reaction proceeds through a carbonium ion, formed from the olefin or alcohol which attacks the nitrogen of the nitrile group. Hydrolysis and tautomerism of the intermediate product leads to formation of the N-substituted amide.

Since an unsaturated nitrile contains both a nitrile group and a double bond, there is the possibility of interaction between these groups. Ritter[2f] carried out such a reaction between acrylonitrile (AN) and sulfuric acid in the presence of acetic acid and represented the polymer obtained as polyalanine (I) in the absence of any evidence.

$$CH_2{=}CHCN \xrightarrow{H_2SO_4} CH_2{=}CHCO[NHCH(CH_3)CO]_nNHCH(CH_3)CN$$
I

Formation of I is possible if propagation of the polymerization is through the α-carbon atom of the nitrile. Magat[10] reported the formation of a soluble polymer, of unidentified structure, on reaction of methacrylonitrile with a large excess of sulfuric acid.

The reaction of α,β-unsaturated nitriles with concentrated sulfuric acid seemed therefore to be an interesting method for the preparation of amino acids.

We reinvestigated the reaction between AN and sulfuric acid in the presence of acetic acid.[2f] An insoluble polymer was formed which on acid hydrolysis gave traces of an amino acid which was not alanine.

Owing to the insolubility of the polymer formed under these conditions[2f] we decided to investigate the reaction using excess sulfuric acid to obtain soluble polymers.[10] In fact under these conditions, a water-soluble product was formed. The chromatogram of its hydrolyzate showed several spots, among them a strong one belonging to β-alanine.

The effect of various factors on the yield of β-alanine was studied. The low yields obtained prompted us to try to find out what happened to the major portion of the AN. Distillation of the dilute reaction mixture, before hydrolysis, in the presence of 40% sodium hydroxide solution, was found to evolve ammonia, which was determined quantitatively by titration. The origin of the ammonia is from ammonium salts or possibly acrylamide, formed by total or partial hydrolysis of the nitrile groups, respectively, in the presence of sulfuric acid. Under these distillation conditions β-alanine did not evolve ammonia as opposed to the behavior acrylamide. The amount of the ammonia evolved was calculated as the per cent of "labile nitrogen" obtained at the end of the reaction, out of the initial amount of acrylonitrile introduced.

Increasing the acid concentration from 92 to 98% or the molar ratio of concentrated sulfuric acid (98%) to AN, increased the yield of β-alanine (Table I). The lowering in yield of β-alanine and the increase in the per cent of "labile nitrogen" at the low sulfuric acid concentration seems to be due to the increase in the amount of water present, which leads to extensive hydrolysis.

TABLE I

EFFECT OF VARIOUS FACTORS ON THE YIELD OF β-ALANINE

$[H_2SO_4]$/[AN][a]	Acid concn, %	β-Alanine yield, %	"Labile nitrogen," %
1	98	2.5	75.0
2.5	98	13.5	78.5
6	98	14.3	77.5
11.25	98	17.5	82.0
2.5	92	5.5	
7.5	92	2.9	96.5
10	92	3.0	97.0
b		5.5	60.0
b		5.2	65.0
c		0.6	

[a] 150 mmol of AN was used. [b] AN–chlorosulfonic acid–sulfuric acid (1:3:1) was used. [c] AN–sulfuric acid–acetic acid (1:2.5:1) was used.

We investigated the reaction of AN with a mixture of sulfuric acid and chlorosulfonic acid hoping to increase the yield of β-alanine by eliminating the water present in the reaction mixture. However, the yield decreased (Table I), but there was also a decrease in the per cent of "labile nitrogen." We tried also the reaction conditions of Ritter,[2f] using a mixture of sulfuric acid and acetic acid, but in the presence of the latter a large decrease in yield of β-alanine was observed (Table I).

The results of these experiments pointed out that the maximum yield of β-alanine will be obtained using concentrated sulfuric acid or by using fuming sulfuric

(1) Address correspondence to this author at the Department of Chemistry, The University, Tel Aviv, Israel.

(2) (a) J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045 (1948); (b) J. J. Ritter and J. Kalish, *ibid.*, **70**, 4048 (1948); (c) F. R. Benson and J. J. Ritter, *ibid.*, **71**, 4128 (1949); (d) L. W. Hartzel and J. J. Ritter, *ibid.*, **71**, 4130 (1949); (e) R. M. Lusskin and J. J. Ritter, *ibid.*, **72**, 5577 (1950); (f) H. Plout and J. J. Ritter, *ibid.*, **73**, 4076 (1951).

(3) E. M. Smoline, *J. Org. Chem.*, **20**, 295 (1955).

(4) E. T. Roe and D. Swern, *J. Amer. Chem. Soc.*, **77**, 5408 (1955).

(5) R Jacquier and H. Cristol, *Bull. Soc. Chim. Fr.*, 596 (1957).

(6) C. L. Parris and R. M. Christenson, *J. Org. Chem.*, **25**, 331 (1960).

(7) T. Clark, J. Devine, and D. W. Dicker, *Abura Kagaku*, **41**, 78 (1964).

(8) F. L. Ramp, *J. Polym. Sci., Part A*, **3**, 1877 (1965).

(9) I. Weil, R. G. Goebel, E. R. Tulp, and A. Cahn, *Amer. Chem. Soc. Div. Petrol. Chem., Preprints*, **8**, 95 (1963); *Chem. Abstr.*, **62**, 1562 (1965).

(10) E. E. Magat, U. S. Patent 2,628,216 (Feb 10, 1953); *Chem. Abstr.*, **47**, 5129 (1953).

TABLE II
REACTION OF ACRYLONITRILE WITH OLEUM (30% SO_3)

Oleum, mmol[a]	[Oleum]/[AN]	β-Alanine yield, %	α-Sulfo-β-aminopropionic acid, %	"Labile nitrogen," %
450	3	2.7	1.8	
1125	7.5	5.6	6.3	53
1350	9	4.8	2.9	53
1920	12.8	1.9	1.1	59

[a] Equivalent to sulfuric acid.

acid. This led us to carry out experiments using oleum (30% SO_3) (Table II).

It is seen that the yield of β-alanine decreased considerably on using oleum instead of sulfuric acid. On the other hand, the chromatograms showed the formation in relatively high quantity, of a new amino acid, having a smaller R_f than β-alanine, besides that of very small amounts of other amino acids, one of which was identified as taurine by an amino acid analyzer. This amino acid was identified as α-sulfo-β-aminopropionic acid. It was also obtained using 98% sulfuric acid but in very small amounts.

The formation of α-sulfo-β-amino acids by the reaction of α,β-unsaturated nitriles with oleum seemed to be a general reaction. Thus, with methacrylonitrile (MAN) the results in Table III were obtained.

TABLE III
REACTION OF METHACRYLONITRILE WITH SULFURIC ACID OR OLEUM

Acid (mmol)	[Acid]/[MAN]	β-Aminoisobutyric acid yield, %	α-Sulfo-β-aminoisobutyric acid yield, %	"Labile nitrogen," %
H_2SO_4 (480)	4	3.9	4.3	85
Oleum (1125)	9.4	12.8	8.8	61

The amino acids isolated were identified as β-aminoisobutyric acid and α-sulfo-β-aminoisobutyric acid. The chromatograms showed the presence of traces of other amino acids.

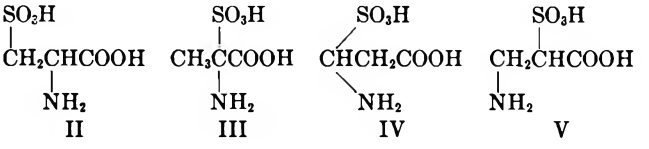
In a similar reaction of crotononitrile with concentrated sulfuric acid, β-aminobutyric acid was obtained in 9.7% yield, whereas with oleum (30% SO_3), it was obtained in 1.2% yield; besides a sulfoamino acid was obtained in 3.9% yield which was not isolated. This amino acid, by analogy to the other sulfoamino acids obtained, seems to be α-sulfo-β-aminobutyric acid.

The infrared spectra of the products obtained before hydrolysis from AN or MAN on reaction with concentrated sulfuric acid or oleum did not show the characteristic absorption peak for the nitrile group, but showed the characteristic absorptions for amide groups and for the $-SO_3H$ group at 1310, 1210–1240, and 1045 cm^{-1}. These products on being dried became insoluble in water and other solvents. Their elementary analysis showed that their composition was not constant and differed from batch to batch.

Establishing the Structure of the Amino Acids.—β-Alanine and α-sulfo-β-aminopropionic acid were isolated by ion exchange technique. The structure of β-alanine was proved from melting point and mixture melting point determinations, elementary analysis, chromatography from various solvent mixtures using authentic β-alanine as a marker, its infrared spectrum, and formation of its N-carbobenzoxy derivative.

The structure of α-sulfo-β-aminopropionic acid (V) was proved as follows. Its elementary analysis showed it to have the empirical formula $C_3H_7NO_5S$, the same as that of cysteic acid. It was soluble in water and had a strongly acid reaction. Potentiometric titration in 0.1 *N* sodium chloride solution with 0.2 *N* sodium hydroxide or 0.2 *N* hydrochloric acid gave a molecular weight of 167 (calcd 169). The pK_a of the various groups in comparison with cysteic acid[11] were as follows: cysteic acid, $pK_a^1 = 1.12$, $pK_a^2 = 1.88$, $pK_a^3 = 8.7$; α-sulfo-β-aminopropionic acid, $pK_a^1 < 2$, $pK_a^2 = 2.8$, $pK_a^3 = 8.7$. Chromatographically the amino acid was different from cysteic acid. In high voltage electrophoresis (1000 V) using a buffer solution (pH 2.6), it migrated in the opposite direction to β-alanine and in the same direction as cysteic acid. The migration was smaller than that of cysteic acid (2.8 and 5.4 cm, respectively). This proves further that the amino acid is acidic, but less than cysteic acid.

Now the four sulfoaminopropionic acids (II–V), which have the empirical formula $C_3H_7NO_5S$, are possible. Structure II is that of cysteic acid. Structures III and IV are those of α-aminosulfonic acids, and it is known[12] that such amino acids are completely unstable in acid solution, and if present could not have remained after a long acid hydrolysis. Therefore, the structure of the sulfoamino acid is V, namely α-sulfo-β-aminopropionic acid. This amino acid will exist mostly in the form of a zwitterion between the sulfonic acid group and the amino group, since the less acidic carboxyl group is the same distance apart from the amino group as is the sulfonic group. That is why this amino acid is expected to be less acidic than cysteic acid, as found.



The traces of taurine found in some of the acid hydrolyzates may be the result of decarboxylation of traces of α-sulfo-β-aminopropionic acid.

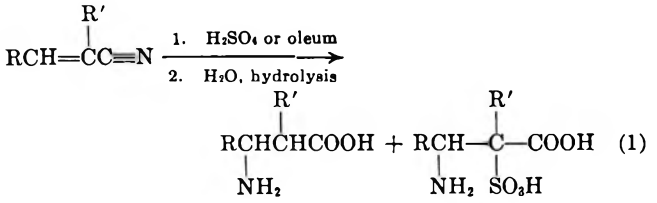
α-Sulfo-β-aminopropionic acid was prepared previously in low over-all yield using a multistep synthesis starting from β-alanine.[13] Our present one-step synthesis from AN is simpler. The structures of β-aminoisobutyric acid and α-sulfo-β-aminoisobutyric acid formed from MAN were established using similar evidence and reasoning as in the case of the amino acids obtained from AN.

Discussion

The reaction of α,β-unsaturated nitriles with concentrated sulfuric acid (or oleum) was shown to lead to the formation of a product which on subsequent acid

(11) C. L. Andrews and A. Schmidt, *J. Biol. Chem.*, **73**, 655 (1927).
(12) P. Moses, Ph.D. Thesis, The Hebrew University of Jerusalem, 1959.
(13) A. Schöberl and H. Braun, *Ann.*, **542**, 274 (1939); S. Gabriel, *Ber.*, **38**, 642 (1905).

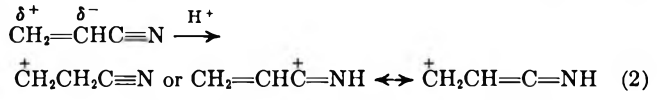
hydrolysis gave a mixture of β-amino acids and α-sulfo-β-amino acids. The reaction may be schematically shown as in eq 1. This course of the reaction is



(1)

different from that given by Ritter.[2f] The reaction between α,β-unsaturated nitriles and concentrated sulfuric acid or oleum is quite complex. The fact that a high percentage of the nitrogen of the nitrile group is converted into "labile nitrogen" shows that hydrolytic (60–95%) reactions of the nitrile groups to ammonia or primary amide groups are very prominent, especially in the more dilute sulfuric acid solutions. For this reason the total yield of amino acids obtained in the reaction (after hydrolysis) did not exceed 20%. Because of this the structure of the product of the reaction, before hydrolysis, is expected to be very complex, and not to have exactly the same structure from batch to batch.

The reactions in eq 2–4 may describe the formation of β-alanine from AN in the presence of sulfuric acid. It seems that formation of a carbonium ion on the β carbon atom of AN is a prerequisite for the formation of β-alanine, and it is plausible that this could occur under the reaction conditions. This carbonium ion may be formed either by electrophilic addition of a proton to the double bond or by protonation of the nitrile group (eq 2). The β-carbonium ion can then



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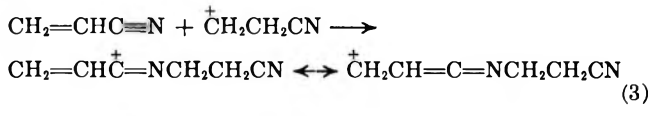
add to a free nitrile group of AN. This reaction may



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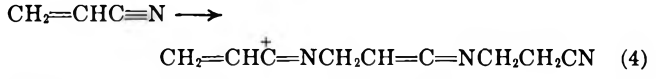

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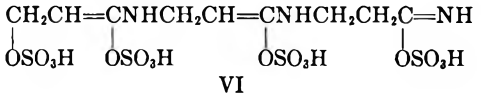
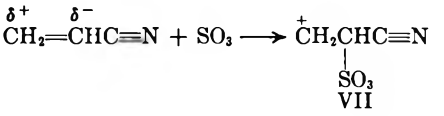
continue. Addition of sulfuric acid to the C=N double bond will yield VI, which on subsequent acid hydrolysis will give β-alanine.



VI

Addition of sulfuric acid to the nitrile group and subsequent hydrolysis can explain why the hydrolysis reaction was so dominant.

The formation of α-sulfo-β-aminopropionic acid can be also explained in terms of electrophilic addition to the double bond. In concentrated sulfuric acid, and of course in oleum, there exists the electrophilic molecule SO_3[14] which adds to the nucleophilic double bond forming a C–S bond, which, contrary to C–O–S bonds, is stable to acid hydrolysis. The fact that with oleum the yield of the sulfonic acid increased gives support to the electrophilic addition of the SO_3 to the double bond.



VII

The β-carbonium ion (VII) can add to the nitrile group of AN, as described before, leading in a series of addition reactions and subsequent hydrolysis to the formation of the α-sulfo-β-amino acid besides β-alanine.

These mechanisms apply equally well to the formation of the other β-amino acids and α-sulfo-β-amino acids from α,β-unsaturated nitriles. They are also consistent with the approved mechanism for the Ritter reaction,[3,9] according to which it is improbable that the propagation will proceed through the α-carbon atom of the nitrile to give poly-α-amino acids but only through the β-carbon atom to give poly-β-amino acids. However, the formation of products having partial structures of polymers or oligomers of β-amino acids, formed by "polymerization" of the α,β-unsaturated nitrile through the nitrile group as shown, is not the dominant reaction, since most of the monomer suffers hydrolysis of the nitrile groups in the course of the reaction, and only unhydrolyzed nitrile groups can participate in the poly-β-amino acid formation.

Experimental Section

Reaction of Acrylonitrile with Sulfuric Acid.—The reaction was carried out under anhydrous conditions and in an argon atmosphere. Redistilled purified dry AN[15] (8 g, 0.15 mol) was added dropwise with stirring to cooled concentrated sulfuric acid (98%, 25 ml), such that the temperature of the reaction mixture did not exceed 10°. The mixture was stirred at room temperature for 24 hr, ice water was added to stop the reaction, and the mixture was diluted to 225 ml so that the acid concentration was 4 *N*, and the solution was refluxed for 24 hr to affect hydrolysis. The hydrolyzate was neutralized with solid barium hydroxide and centrifuged from barium sulfate. The amount of the amino acids present in the filtrate was determined by paper chromatography. The reactions with methacrylonitrile and crotononitrile were carried out similarly.

α-Sulfo-β-aminopropionic Acid.—Acrylonitrile was added dropwise with stirring at the rate of about 0.4 ml every half minute to 25 ml of oleum (30% SO_3) cooled in an ice bath. The temperature rose to about 70° and was kept there until the end of the addition. The reaction mixture was stirred at room temperature for 24 hr, diluted with ice water until the concentration of the acid was 5 *N*, and refluxed for 24 hr to affect hydrolysis. The solution was neutralized with the calculated amount of solid barium hydroxide, and centrifuged from barium sulfate. The supernatent solution was stirred for 3 hr with Dowex 50W (H^+, 25 g) and filtered. The filtrate was evaporated to dryness *in vacuo*, and α-sulfo-β-aminopropionic acid crystallized out on standing under absolute ethanol. It was recrystallized from water–absolute ethanol to yield 1.6 g (6.3%): mp 250–260° dec; R_f (descending from butanol–acetic acid–water) 0.13 (cysteic acid, R_f 0.11). The nmr spectrum in D_2O showed a doublet centered at 3.53 ($-CH_2-$) and a triplet centered at 4.15 ppm ($-CH-$). *Anal.* Calcd for $C_3H_7NO_5S$: C, 21.30; H, 4.17; N, 8.28; S, 18.96. Found: C, 21.30; H, 4.10; N, 8.67; S, 18.40.

β-Alanine.—The Dowex resin left from the isolation of α-sulfo-β-aminopropionic acid was suspended in 1% ammonia solution (120 ml) and stirred for 1 hr to extract the β-alanine. The extract was evaporated to dryness *in vacuo*, and the β-alanine crystallized out on standing under absolute ethanol. It was recrystallized from water–dry acetone, yield 0.5 g (3.7%).

(14) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 299.

(15) C. H. Bamford and A. D. Jenkins, *Proc. Roy. Soc.* (London), **A216**, 515 (1953).

Isolation of the Product of Reaction between Acrylonitrile and Sulfuric Acid.—The diluted reaction mixture before hydrolysis was neutralized with solid barium hydroxide and centrifuged from the precipitated barium sulfate. The precipitate was extracted with hot water. The filtrate and extract were combined, Dowex 50W (H^+, 25 g) was added to remove excess barium ions, if present, and other basic materials and the mixture was stirred for 3 hr. The filtrate from the ion-exchange resin was evaporated to dryness *in vacuo*, and the residue solidified on standing under absolute ethanol. In the reaction between AN (0.15 mol) and 98% sulfuric acid (0.48 mol), 9.8 g of a product were obtained. *Anal.* Found: C, 45.09; H, 7.64; N, 12.70; S, 1.66%.

In the reaction between acrylonitrile (0.15 mol) and oleum (30% SO_3) (1.125 mol), 10.2 g of a product were obtained. *Anal.* Found: C, 33.35; H, 5.43; N, 9.70; S, 12.90%.

α-Sulfo-β-aminoisobutyric Acid.—The reaction mixture obtained from methacrylonitrile (8 g, 0.12 mol) and oleum (30% SO_3, 25 ml), was diluted with ice water to 225 ml and refluxed for 24 hr. It was neutralized with barium hydroxide, centrifuged, and stirred with Dowex 50W (25 g) for 3 hr. The filtrate was evaporated to dryness *in vacuo*, and the residue was dissolved in hot ethanol (10 ml) and precipitated by diluting with dry acetone, scratching, and cooling in liquid air; a crude yield of 2.8 g (12.7%) was obtained. α-Sulfo-β-aminoisobutyric acid was recrystallized from ethanol–acetone: mp 240° dec; R_f 0.16 (descending from butanol–acetic acid–water). The nmr spectrum in D_2O showed only absorptions at 1.52 ($-CH_3$) and 3.45 ppm ($-CH_2-$). *Anal.* Calcd for $C_4H_9NO_6S$: C, 26.23; H, 4.92; N, 7.65; S, 17.49. Found: C, 26.37; H, 4.80; N, 8.00; S, 17.95.

β-Aminoisobutyric Acid.—The Dowex resin left from the isolation of α-sulfo-β-aminoisobutyric acid was suspended in 1% ammonia solution (150 ml) stirred for 1 hr and filtered. The filtrate was evaporated to dryness *in vacuo*, and the residue was extracted by hot absolute ethanol. The insoluble β-aminoisobutyric acid was filtered and washed with acetone. Another crop of the product was obtained on addition of acetone to the filtrate to give a total yield of 0.24 g (2%). It was recrystallized from ethanol–acetone.

Quantitative Determination of the Amino Acids by Paper Chromatography.—The descending method of paper chromatography was used and the developing solvent was composed of *n*-butyl alcohol–acetic acid–water (25:6:25). The chromatograms were sprayed with 0.5% ninhydrin solution in 85% aqueous acetone. Spots from the unknown as well as from markers were eluted with 75% aqueous ethanol and their absorbancy at 565 mμ was measured.

Registry No.—Sulfuric acid, 76649-93-9; acrylonitrile, 107-13-1; methacrylonitrile, 126-98-7; β-alanine, 107-95-9; IV, 15924-28-4; β-aminoisobutyric acid, 144-90-1; α-sulfo-β-aminoisobutyric acid, 15924-29-5.

Hydrogenation of Conjugated Diolefins with Transition Metal π Complexes

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It has already been found by Sloan, Matlack, and Breslow[1] that a number of transition metal compounds combined with organometallic derivatives are soluble catalysts for the hydrogenation of olefins such as cyclohexene, 1-octene, 2-pentene, etc. Transition metals in groups IV–VIII, mostly as acetylacetonates or as alkoxides, have been found to be active when combined with, preferably, a trialkylaluminum compound. Mono-, di-, tri-, and tetrasubstituted olefins have been hydrogenated. They postulated the mechanism for the hydrogenation with the soluble catalysts as follows.

The reaction of transition metal derivatives with aluminum alkyls has as its first step alkylation of the transition metal derivative (eq 1). This step is followed by hydrogenolysis of the metal–alkyl bond formed to yield a metal hydride (eq 2), which then adds to an olefin forming a new metal alkyl (eq 3). Hydrogenolysis of the latter yields saturated hydrocarbon with regeneration of the metal hydride (eq 4).

$$R_3Al + MX_n \longrightarrow R_2AlX + RMX_{n-1} \quad (1)$$

$$RMX_{n-1} + H_2 \longrightarrow RH + HMX_{n-1} \quad (2)$$

$$>C{=}C< + HMX_{n-1} \rightleftharpoons HC{-}C{-}MX_{n-1} \quad (3)$$

$$H{-}C{-}C{-}MX_{n-1} + H_2 \longrightarrow HC{-}CH + HMX_{n-1} \quad (4)$$

The hydrogenation of olefins by Ziegler catalysts was also investigated by Heck,[2] who postulated insertion reaction mechanisms of metal complexes. On the other hand, selective hydrogenation of conjugated diolefins, such as butadiene to monoolefins (butene-1, butene-2) by pentacyanocobaltate (II) complexes was studied by Kwiatek.[3]

In this paper, hydrogenation of butadiene or isoprene by binary catalysts systems of transition metal π complexes and organometallic compounds was studied. Transition metal π complexes tried were biscyclopentadienyl transition metal dichloride (Cp_2TiCl_2, Cp_2VCl_2, and Cp_2ZrCl_2), π-allyl-π-cyclopentadienylnickel ($C_5H_5NiC_3H_4$), cyclopentadienyldicarbonylcobalt ($CpCo(CO)_2$), and cyclopentadienyldicarbonylchloroiron $CpFe(CO)_2Cl$. Organometallic compounds used were organolithium compounds (for example, n-C_4H_9Li), Grignard reagents (for example, PhMgBr), and organoaluminum compounds ($AlEt_3$, $AlBu_3$).

The results are shown in Tables I–III. In Table I, the results of hydrogenation of butadiene by biscyclopentadienyl transition metal dichlorides are shown. In Cp_2TiCl_2–BuLi (or PhMgBr) catalyst systems, quantitative hydrogenation of butadiene to saturated hydrocarbon (butane) was observed, and little unsaturation

TABLE I

HYDROGENATION OF BUTADIENE BY BISCYCLOPENTADIENYL TRANSITION METAL COMPOUNDS[a]

Catalyst system	Conversion, %	Content, %			
		Butene-1	*cis*-Butene-2	*trans*-Butene-2	Butane
Cp_2TiCl_2–BuLi	100.0	0	0	0	100.0
Cp_2TiCl_2–PhMgBr	99.0	0	0.2	2.3	97.5
Cp_2VCl_2–BuLi	62.2	2.3	13.9	84.8	0
Cp_2VCl_2–PhMgBr	43.1	1.7	26.1	72.2	0
Cp_2ZrCl_2–BuLi	0				
Cp_2ZrCl_2–PhMgBr	0				

[a] The hydrogenation reactions were carried out at 40–45° for 15 hr using the catalyst system 2 mmol of Cp_2MCl_2 (M: Ti, V, Zr) and 4.8 mmol of BuLi (or 7 mmol of PhMgBr) and 50 ml of benzene as the solvent. The initial hydrogen pressure was 60 kg/cm²; 7 ml of butadiene was used in each experiment.

(1) M. F. Sloan, A. S. Matlack, and David S. Breslow, *J. Amer. Chem. Soc.*, **85**, 4014 (1963).

(2) R. F. Heck, Advances in Chemistry Series, No. 49, American Chemical Society, Washington, D. C., 1965, p 181.

(3) J. Kwiatek and J. K. Seyler, Advances in Chemistry Series, No. 37, American Chemical Society, Washington, D. C., 1963, p 201.

TABLE II

SELECTIVE HYDROGENATION OF ISOPRENE BY BISCYCLOPENTADIENYLVANADIUM DICHLORIDE[a]

		Content, %			
Catalyst system	Conversion, %	2-Methyl-1-butene	2-Methyl-2-butene	2-Methyl-1-butene	2-Methylbutane
Cp_2VCl_2–BuLi	100.0	5.8	92.1	2.1	0
Cp_2VCl_2–PhMgBr	97.8	4.9	93.7	1.4	0

[a] The hydrogenation reactions were carried out at 95–100° for 15 hr using the catalyst system 2 mmol of Cp_2VCl_2 and 4.8 mmol of BuLi (or 7 mmol of PhMgBr) and 50 ml of benzene as the solvent. The initial hydrogen pressure was 60 kg/cm²; 7 ml of isoprene was used in each experiment.

TABLE III

HYDROGENATION OF BUTADIENE BY MONOCYCLOPENTADIENYL TRANSITION METAL COMPOUNDS[a]

		Content, %			
Catalyst system	Conversion, %	Butene-1	*cis*-Butene-2	*trans*-Butene-2	Butane
$CpNiC_3H_7$–$AlEt_3$	72.7[b]	7.4	30.2	42.3	20.1
$CpNiC_3H_7$–PhMgBr	86.4	0.9	41.2	48.0	9.9
$CpCo(CO)_2$–$AlEt_3$	91.7	0.5	40.5	51.4	7.3
$CpCo(CO)_2$–PhMgBr	87.4	4.7	44.2	48.3	2.8
$CpFe(CO)_2Cl$–$AlEt_3$	98.8	2.1	45.6	52.3	0
$CpFe(CO)_2Cl$–PhMgBr	85.3	1.0	44.7	44.3	0

[a] The hydrogenation reactions were carried out at 40–45° for 6 hr using the catalyst system 2 mmol of $CpNiC_3H_7$, $CpCo(CO)_2$, or $CpFe(CO)_2Cl$ and 4.8 mmol of $AlEt_3$ (or 7 mmol of PhMgBr) and 50 ml of benzene as a solvent. The initial hydrogen pressure was 60 kg/cm²; 7 ml of butadiene was used in each experiment. [b] Cyclooligomerization also occurred.

was contained in the reaction products. On the other hand, in Cp_2VCl_2–BuLi (or PhMgBr) catalyst systems, selective hydrogenation of conjugated diene to monoolefin was observed, and further hydrogenation of monoolefin (butenes) to butane was not observed. In Cp_2ZrCl–BuLi (or PhMgBr) catalyst systems, no hydrogenation reaction was observed. In any case of Cp_2MCl_2 (where M is Ti, V, or Vr)–$AlEt_3$ (or $AlBu_3$) catalysts systems, or in any case of Cp_2M, $Cp_2M^+X^-$ (where M is Ni, Co, or Fe)–organometallic compound (BuLi, PhMgBr, $AlEt_3$, $AlBu_3$) catalyst systems, no hydrogenation reaction was observed.

In Table II, the results of selective hydrogenation of isoprene by Cp_2VCl_2–BuLi (or PhMgBr) catalyst system are shown. The reaction products were 2-methyl-1-butene, 2-methyl-2-butene (main product), and 3-methyl-1-butene. Further hydrogenation of monoolefins to 2-methylbutane was not observed. In Table III, the results of hydrogenation of butadiene by $CpNiC_3H_7$ (or $CpCo(Co)_2$, $CpFe(CO)_2Cl$)–$AlEt_3$ (or PhMgBr) catalysts system are shown. Under the reaction conditions (reaction temperature of 40–45°, reaction time of 6 hr), butene-1 and butene-2 were mainly produced, and butane constituted only a small portion of the reaction products, but by extending the reaction time to 15 hr or using a higher reaction temperature further hydrogenation of butene to butane occurred and the butane content increased.

From the above experimental results, we presume the following: Cp_2TiCl_2 (or Cp_2VrCl_2, Cp_2ZrCl_2) could be alkylated by BuLi (or RMgBr) to form a metal–alkyl bond which could be hydrogenated to yield a metal hydride. Catalytic activity for hydrogenation is mostly dependent on the nature of the center element of the π complex (T $\gg$ V $\gg$ Zr). The π complex of titanium can catalyze the hydrogenation of monoolefins to saturated hydrocarbons, whereas the π complex of vanadium can catalyze the hydrogenation of conjugated dienes to monoolefins, being unable to hydrogenate monoolefins to saturated hydrocarbons. The π complex of zirconium has no catalytic effect on hydrogenation. On the other hand, neither Cp_2M nor $Cp_2M^+X^-$ (where M is Ni, Co or Fe) could be alkylated to form a metal–alkyl bond. These π complexes have no catalytic power on the hydrogenation. By the reaction of $CpNiC_3H_5$ (or $CpCo(CO)_2$, $CpFe(CO)_2Cl$) and $AlEt_3$ (or PhMgBr), a metal–alkyl bond would be formed, which would be followed by hydrogenolysis to yield the metal hydrides. Transition metal compounds of Ni, Co, and Fe themselves can catalyze the hydrogenation of monoolefins to saturated hydrocarbons, but hydrogenation was greatly retarded by coordination from the cyclopentadienyl ligand.

Experimental Section

The hydrogenation reactions were carried out in an autoclave (100 ml), and all opeations were carried out in a nitrogen atmosphere. In general, 2 mmol of a transition metal π complex, 4.8 mmol (or 7 mmol) of an organometallic compound, 50 ml of benzene as solvent, and 7 ml of butadiene (or isoprene) were taken in the autoclave under a nitrogen atmosphere. Hydrogen was then introduced up to 60 kg/cm². The reactions were carried out at 40–45° (or at 95–100°) for 15 hr (or for 6 hr) under strong agitation. The products were analyzed by isolation and were identified or determined by gas chromatography.

Preparation of Transition Metal π Complexes.—Cyclopentadienyldicarbonylcobalt(I), $CpCo(CO)_2$, was prepared[4] by treating a twofold excess of dicobalt octacarbonyl with cyclopentadiene at room temperature. π-Allyl-π-cylopentadienylnickel was prepared[5] by treating Cp_2Ni with allylmagnesium chloride in THF under an inert atmosphere. Cyclopentadienyldicarbonylchloroiron(I) $CpFe(CO)_2Cl$ was prepared[4] by oxidizing cyclopentadienyltetracarbonyliron $(CpFe)_2(CO)_4$ with air in HCl acidic ethanol–chloroform solution.

Cyclopentadienyltetracarbonyliron, $(CpFe)_2(CO)_4$; nickelocene, Cp_2Ni;[6] biscyclopentadienyltitranium dichloride, Cp_2TiCl_2;[7] biscyclopentadienylvanadium dichloride, Cp_2VCl_2; and biscyclopentadienylzirconium dichloride, $Cp\ ZrCl_2$,[8] were prepared by the procedure as described in the literature.

Registry No.—Cp_2TiCl_2, 1271-19-8; Cp_2VCl_2, 12083-48-6; Cp_2ZrCl_2, 1291-32-3; $Cp_2NiC_3H_7$, 12107-46-9; $CpCo(CO)_2$, 12078-23-8; $CpFe(CO)_2Cl$, 12107-04-9; butadiene, 106-99-0; isoprene, 78-79-5.

(4) T. S. Piper, *J. Inorg. Nucl. Chem.*, **1**, 165 (1955).
(5) W. R. McCallan, *J. Amer. Chem. Soc.*, **83**, 1601 (1961).
(6) C. L. Hobbs, British Patent 733,129 (1955).
(7) G. Wilkinson and J. M. Birmingham, *J. Amer. Chem. Soc.*, **76**, 4281 (1934).
(8) G. Wilkinson and F. A. Cotton, *Chem. Ind.* (London), 307 (1954).

Cyclopropanecarboxylic Acid Fluoride. An Improved Synthesis

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Cyclopropanecarboxylic acid fluoride was reported previously[1] to be obtained in 30% yield by the action of potassium fluoride on cyclopropanecarboxylic acid chloride and in 54% yield by allowing the free acid to

(1) M. Hanack and H. Eggensperger, *Chem. Ber.*, **96**, 1341 (1963).

react with a mixture of benzoyl chloride and potassium fluoride.

We have found that, when 4-chlorobutyryl chloride is treated with potassium fluoride at 195–200° in a suitable reaction medium such as tetramethylene sulfone, cyclopropanecarboxylic acid fluoride is produced directly in 70% yield (eq 1). Since 4-chlorobutyryl

$$Cl(CH_2)_3COCl + 3KF \rightarrow \text{(cyclopropanecarboxylic acid fluoride)} + KHF_2 + 2KCl \quad (1)$$

chloride is easily made from γ-butyrolactone and thionyl chloride,[2a,b] this approach appears to offer a practical route to the acyl fluoride and its many derivatives.

We have evidence to show that the reaction proceeds in two distinct steps which, at the optimum elevated temperature, are practically concerted. First there is an exothermic exchange of the acyl halogen atom, followed by a base-induced cyclization, to give the product observed.

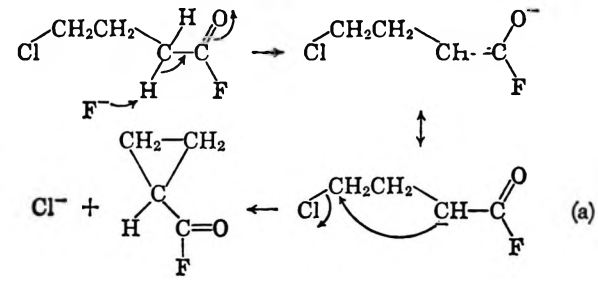
The first step in the reaction is the exchange of the acyl halogen for fluorine. This was demonstrated by running the reaction at various temperatures. At 130° the sole product is 4-chlorobutyryl fluoride. This product may be recovered and distilled or, simply by raising the temperature in the reaction flask to 190–195°, it may be converted into cyclopropanecarboxylic acid fluoride. Below 190° no cyclic product was observed. It was further noted that, when 4-chlorobutyryl chloride was added to the potassium fluoride–tetramethylene sulfone slurry, an exothermic reaction took place, resulting in a temperature rise of about 10° in the reaction flask. As no similar increase in temperature occured when the acid chloride was mixed with the sulfone alone, the results noted above must be due to the initial exchange reaction.

Whereas halogen exchange reactions brought about by potassium fluoride are well known,[3,4] its use as a base has been more limited. The basic properties of potassium fluoride were noted first in 1948[5] by Nesmayanov and his colleagues, who discovered that the reaction in eq 2 did not proceed as anticipated. In-

$$CCl_3COOH + 3KF \not\rightarrow CF_3COOH + 3KCl \quad (2)$$

stead, a base-induced decarboxylation was observed, with the formation of chloroform and carbon dioxide. Prior to this, it was thought that more powerful nucleophiles, such as amines or hydroxides, were required for this type of reaction. Further examples of the use of potassium fluoride as a base have been summarized recently.[6] The second stage of the reaction, then, may be written simply as the abstration of an α proton, followed by an intramolecular nucleophilic displacement, resulting in ring closure (see Scheme I).

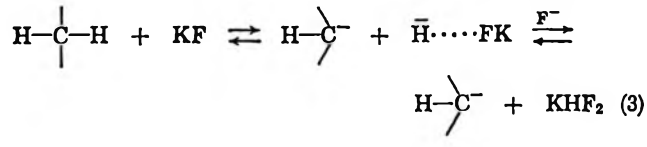
SCHEME I



(a)

$$HF + KF \rightarrow KHF_2 \quad (b)$$

It has been suggested[7] that potassium fluoride is not a strong enough nucleophile to react with an α-hydrogen atom, *e.g.*, in adipic acid, but this reasoning may not apply here because the α hydrogen is rendered relatively acidic by the acyl fluorine atom. The importance of the acyl fluorine atom is shown by the fact that efforts to cyclize 4-chlorobutyronitrile, 4-chlorobutyranilide, and ethyl 4-chlorobutyrate by heating with potassium fluoride were unsuccessful. It is interesting to note that 4-chlorobutyronitrile can be cyclized by heating with sodium hydroxide[8] and that a mixture of ethyl 4-iodobutyrates gives good yields of ethyl cyclopropanecarboxylate[9] when heated with sodium hydride, indicating that very strong bases are required in the absence of the unique activating influence present in the acyl fluoride. It is also possible that initially there is formed a strong hydrogen bond (see eq 3) followed by formation of KHF_2 and



(3)

a carbanion. The incipient carbanion in both cases would have resonance stabilization through the enolate form, and could subsequently cyclize. Fluoride ions are capable of forming the strongest known hydrogen bonds,[10] *i.e.*, F^- acting as a Lewis base and it has been shown[11,12] that active methylene compounds are suitable donors.

In both reaction schemes the strength of HF_2^- acts as a driving force in the reaction and its formation ties up excess acid, to which the product is sensitive.[13]

In a brief examination of the ability of other alkali metal fluorides to bring about the cyclization, we carried out the reaction with cesium fluoride and with sodium fluoride. The former, as expected, gave the cyclopropanecarboxylic acid fluoride, but only in the same yield (70%) as potassium fluoride. Sodium

(2) (a) W. Reppe, *Ann. Chem.*, **596**, 1 (1955). (b) $Cl(CH_2)_3COCl$ is also available from Aldrich Chemical Co.

(3) M. Hudlický, "Chemistry of Organic Fluorine Compounds," The Macmillan Co., New York, N. Y., 1962, p 87 ff.

(4) A. K. Barbour, L. J. Belf, and M. W. Buxton, *Advan. Fluorine Chem.*, **3**, 181 (1963).

(5) A. N. Nesmayanov, K. A. Pecherskaya, and G. Y. Uretskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 240 (1948).

(6) L. Rand, D. Haidukewych, and R. J. Dolinski, *J. Org. Chem.*, **31**, 1272 (1966).

(7) L. Rand, W. Wagner, P. O. Warner, and L. R. Kovac, *ibid.*, **27**, 1034 (1962).

(8) C. M. McCloskey and G. H. Coleman in "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 221.

(9) B. W. Horrom and L. R. Swett (Abbott Laboratories), U. S. Patent 2,992,269(July 11, 1961).

(10) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p 460.

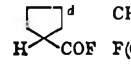
(11) A. Allerhand and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **85**, 1233, 1715 (1963).

(12) E. LeGoff, *ibid.*, **84**, 3975 (1962).

(13) If the crude product is left to stand overnight it decomposes to a certain extent. This is thought to be due to traces of HF carried over by the product. Although the decomposition temperature of KHF_2 is given as 225°, it is an equilibrium and probably occurs to a limited extent at 200°.

TABLE I

PREPARATION OF CYCLOPROPANECARBOXYLIC ACID FLUORIDE AND 4-CHLOROBUTYRYL FLUORIDE[a]

Acyl halide	Mole ratio KF/acyl halide	Reaction medium[b]	Reaction temperature, °C	Product (yield, %)
$Cl(CH_2)_3COCl$	3.86	T	195–200	CH_2CH_2CHCOF (70)
$Cl(CH_2)_3COCl$	2.44	T	195–200	CH_2CH_2CHCOF (70)
$Cl(CH_2)_3COCl$	2.44	N	195–200	CH_2CH_2CHCOF
$Cl(CH_2)_3COCl$	1.94	T	195–200	CH_2CH_2CHCOF (37) + $Cl(CH_2)_3COF$
$Cl(CH_2)_3COCl$	2.44	T	130–140	$Cl(CH_2)_3COF$ (52)
$Cl(CH_2)_3COCl$	4.14[c]	T	197	$Cl(CH_2)_3COF$ (40)
$Br(CH_2)_3COCl$	6.36	N	195–200	CH_2CH_2CHCOF (23)
$Cl(CH_2)_4COCl$	2.69	T	195–200	Not identified
$Br(CH_2)_5COCl$	3.66	T	195–200	 $CH_2=CH(CH_2)_3COF$ $F(CH_2)_5COF$

[a] The low boiling products were distilled from the reaction vessel as they were formed. Where the products were removed by vacuum distillation, a prior reaction time of 1–2 hr was used. [b] T = tetramethylene sulfone; N = N-methylpyrrolidone. [c] NaF. [d] Identified by infrared and nmr spectroscopy and by preparation of the amide, mp 177–178°.

fluoride gave only 4-chlorobutyryl fluoride. This latter result would be expected upon consideration of the base strengths of the alkali metal fluorides.[14]

The scope of the reaction is further illustrated by the conversion of 4-bromobutyryl chloride into cyclopropanecarboxylic acid fluoride and by the use of various "solvents" for the potassium fluoride. We find that tetramethylene sulfone, N-methylpyrrolidone and γ-butyrolactone give satisfactory results, although the first is preferred chiefly because its higher boiling point minimizes contamination of the product. Dimethyl sulfone can be used, but its high melting point (109°) is a serious drawback. When nitrobenzene is the reaction medium, even at temperatures up to 210°, the major product is the open chain chlorobutyryl fluoride, with only minor amounts of the cyclic compound. Therefore, the solubility of the metal fluoride in the reaction medium appears to be an important factor.

Apparently the reaction is limited to 4-halobutyryl halides, since higher homologs do not cyclize readily. Thus, 5-chlorovaleryl chloride did not give any cyclobutanecarboxylic acid fluoride and 6-bromohexanoyl chloride gave, in low yield, a mixture of three products, from which a small amount of cyclopentanecarboxylic acid fluoride could be distilled. The other products were 6-fluorohexanoyl fluoride and 5-hexenoyl fluoride. These results suggest that thermodynamic and energy factors govern the course of the reaction.

Experimental Section

Representative procedures for the preparation of cyclopropanecarboxylic acid fluoride and 4-chlorobutyryl fluoride are given below. The results of other experiments are given in Table I. Tetramethylene sulfone was practical grade, supplied by Distillation Products Industries. Potassium fluoride was Baker and Adamson (2091), finely ground and dried at 160–170°. 4-Bromobutyryl chloride was purchased from K & K labs; all other reagents were obtained from Aldrich Chemial Company.

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Cyclopropanecarboxylic Acid Fluroide.—A 2-l. three-necked, creased flask (Morton type) was fitted with a dropping funnel, thermometer, take-off head with condenser, and a high-speed blade stirrer. Tetramethylene sulfone (500 ml) was placed in the flask and the temperature raised to 195–200°. Dry potassium fluoride (159 g, 2.74 mol) was added and followed, with vigorous stirring, by 4-chlorobutyryl chloride (100 g, 0.71 mol). The rate of addition of the acyl chloride was adjusted so that the temperature in the take-off head was maintained between 80 and 100°. The temperature in the reaction flask rose rapidly to 209° and, after a few minutes, a colorless distillate began to collect. Total addition of the acyl chloride took 50 min. The crude product which had collected was distilled through a 6-in. Vigreux column to give cyclopropanecarboxylic acid fluoride (44 g, 70.4% of theory): bp 81°; n^{25}D 1.3775. The infrared spectrum of the neat liquid showed a strong C=O stretching band at 1842 cm^{-1}. Hanack[1] reports bp 80–81° and C=O stretching at 1840 cm^{-1}. The 60-MHz pmr spectrum showed two complex multiplets, that of the α proton being centered at δ 1.70 ppm from tetramethylsilane. The β protons were less deshielded and appeared at 1.11 ppm. The integrated areas under the multiplets were 1:4.

4-Chlorobutyryl Fluoride.—In a similar manner 100 g (0.71 mol) of 4-chlorobutyryl chloride was treated with 100 g (1.73 mol) of potassium fluoride in tetramethylene sulfone at 130°. An exothermic reaction took place and the temperature rose to 139°. After the addition of the acyl chloride had been completed, the temperature reverted to 130°. The mixture was stirred vigorously for 2 hr, but no distillate collected despite the aid of a nitrogen sweep. The pressure in the system was reduced to about 150 mm, while still maintaining a temperature of 130°. A colorless product was collected, which was redistilled to give 47 g of 4-chlorobutyryl fluoride, bp 60° (100 mm) or 137–139°. Its infrared spectra also had a strong C=O stretching band at 1842 cm^{-1}. The 60-MHz pmr spectrum showed three multiplets: $-CH_2Cl$ at 3.70 ppm from tetramethylsilane, appeared as a triplet, with some unresolved fine structure (J_{HCCH} = 6.5 Hz); $-CH_2COF$ at 2.77 ppm was also a triplet with fine structure (J_{HCCH} = 6.5 Hz); $-CH_2-$ appeared as a pentet with fine structure at 2.16 ppm (J_{HCCH} = 6.5 Hz).

Registry No.—Cyclopropanecarboxylic acid fluoride, 694-02-0; 4-chlorobutyryl fluoride, 15973-66-7.

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The Bromination of Salicylaldimine Chelates with N-Bromosuccinimide[1]

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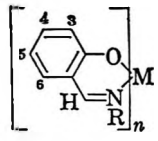
Bis(N-*n*-butylsalicylaldiminato)nickel(II) (I, M = Ni, R = C_4H_9, n = 2) has been reported to form a dibromide upon interaction with N-bromosuccinimide,[2] but some question exists as to whether the substitution occurs at the azomethine carbon[3] or at a ring phenyl position.[4] This substitution is now shown to occur on the ring, principally at the 5 position in agreement with the reactivity of salicylaldehyde[5] and with the observed reactivity of the chelated 2,4-pentanedionates.[2,6] Further interaction of the dibromide with N-bromosuccinimide also produces a tetrabromide which is bis(N-*n*-butyl-3,5-dibromosalicylaldiminato)-nickel(II). These reactions have also been extended to the bromination of the kinetically inert complex tris(N-methylsalicylaldiminato)cobalt(III) (I, M = Co, R = CH_3, n = 3].



The structure of these chelates was demonstrated by analysis, independent synthesis, and by infrared, near infrared-visible, and nmr spectroscopy. The infrared data are in agreement with the indicated substitution with characteristic phenyl hydrogen out-of-plane deformation absorptions of proper intensity found at 750–760 cm^{-1} for the unsubstituted imine chelates, at 815–820 cm^{-1} for the 5-bromo chelates, and at 860 cm^{-1} for the 3,5-dibromo chelates.[7] In each case a strong absorption attributable to the imine C=N stretching frequency was observed at 1615–1630 cm^{-1}.[4] The spectra of chelates prepared by alternate methods were in each case identical. The visible-near infrared spectra of these chelates also were in each case similar to those previously reported for such cobalt(III)[8,9] and nickel(II)[10] complexes.

The nmr data support the assigned structures with the resonances due to the protons *ortho* and *para* to the oxygen having the proper intensity and, where definable, the proper splitting for the indicated substitution. The nickel chelate spectra were all concentration dependent in agreement with the known association of these materials in solution to produce mixtures of diamagnetic monomers having a square planar configuration around the nickel ion and paramagnetic polymeric species.[11,12] This phenomenon is particularly evident in the case of the 5-bromo chelate in which the azomethine proton resonance is shifted 0.58 ppm downfield. Such large shifts are attributable to spin delocalization in a paramagnetic complex and are in agreement with shifts previously observed for paramagnetic salicylaldimine complexes.[13–15] The effect of concentration on the spectra of the unsubstituted and 3,5-dibromonickel chelates is considerably less pronounced with the azomethine proton resonance being shifted downfield only 0.11 and 0.35 ppm over the same concentration range. The large effect found for the 5-bromo derivative is probably due to the electron-withdrawing effect of the bromo group which leaves the chelated nickel(II) ion more electrophilic. The smaller effect noted for the 3,5-dibromo derivative may be due to compensating effects of increased electrophilicity of the nickel ion and steric inhibition of association by the 3 substituent[11] and/or decreased nucleophilicity of the oxygen atoms due to electron withdrawal. Increasing the temperature of a 0.05 *M* deuteriochloroform solution of the 5-bromo derivative from 38 to 58° also shifts the position of the proton resonances, *e.g.*, the azomethine resonance is shifted from −670 to −702 cps, suggesting the additional presence of paramagnetic "tetrahedral" nickel(II) species in these solutions.[13,16] Some spectral evidence was found for both associated and "tetrahedral" species in concentrated benzene solutions of the 5-bromo chelate in the form of a very broad but weak absorption in the near-infrared region which could be resolved into at least two broad peaks with maxima centered approximately at 9500 and 7000 cm^{-1} [14,17] characteristic of "octahedral" and "tetrahedral" species.

Nmr studies on the brominated cobalt(III) complexes showed that in solution, both are diamagnetic indicating that no Co(II) species are present and both are present only in the sterically favorable *trans* stereochemistry around the octahedral cobalt(III) ion.[18] Both of these chelates crystalize as solvates which are only desolvated with difficulty.

Experimental Section

Bromides of Bis(N-*n*-butylsalicylaldiminato)nickel(II).—Bis(N-*n*-butyl-5-bromosalicylaldiminato)nickel(II) was prepared by mixing together an alcoholic solution of 10 g (0.05 mol) of 5-bromosalicylaldehyde and 12 g (0.16 mol) of *n*-butylamine and an aqueous solution of 6 g (0.025 mol) of nickel chloride hexahydrate. The product, after isolation by filtration and drying, was recrystallized from carbon tetrachloride–petroleum ether

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(30–60°). The green needles thus obtained,[19] mp 193–195° [λ_{max}, 620 mμ (ϵ 95 cm^{-1} M^{-1}), benzene, 25°, nmr resonances ($CDCl_3$, 38°, 0.025 M), -N=CH (−626), $-NCH_2$, (−257), *o*-CH (−376), *m,m*-CH, (−433), CH_3CH_2 (−100), $-CH_3$ (−58 cps)] were identical in all respects with the dibromide[2] prepared by the N-bromosuccinimide bromination of bis(N-*n*-butylsalicyaldiminato)nickel(II). This starting chelate had the following resonances ($CDCl_3$, 38°, 0.02 M): -N=CH (−579), NCH_2 (−241), *o*-CH (−386), *p*-CH (−380), *m,m*-CH (−422, −430), CH_2CH_2 (−100), CH_3, (−58 cps).

Bis(N-*n*-butyl-3,5-dibromosalicylaldiminato)nickel(II) was prepared by the reaction of 4.1 g (0.01 mol) of bis(N-*n*-butylsalicylaldiminato)nickel(II) in 30 ml of chloroform with 7.1 g (0.04 mol) of powdered N-bromosuccinimide. After 1 hr the product was isolated by precipitation with petroleum ether, removal of the succinimide by vacuum sublimation at 110°, and recrystallization of the crude product from carbon tetrachloride. The green tetrabromide, mp 214–216° [λ_{max}, 620 mμ (ϵ 107 cm^{-1} M^{-1}), benzene, 25°; nmr resonances (38°, $CDCl_3$, 0.025 M), -NCH, (−556), $-NCH_2$ (−246), *m,m*-CH, (−430, −454), CH_2CH_2 (100), $-CH_3$ (−60 cps)] was identical with a chelate prepared as in the above paragraph using 7 g of 3,5-dibromosalicylaldehyde, 8 g of *n*-butylamine, and 3 g of nickel chloride hexahydrate.

Anal. Calcd for $C_{22}H_{24}Br_4N_2NiO_2$: C, 36.36; H, 3.33; N, 3.86; Ni, 8.08. Found: C, 36.54; H, 3.43; N, 3.72; Ni, 7.63.

Bromination of Tris(N-methylsalicylaldiminato)cobalt(III).—To 1.54 g (0.0032 mol) of tris(N-methylsalicylaldiminato)-cobalt(III),[18] recrystallized from xylene [λ_{max}, 387, 572 sh, 637 mμ sh, (ϵ 8900, 275, $-cm^{-1}$ M^{-1}), benzene, 25°] in 15 ml of chloroform was added 1.8 g (0.01 mol) of powdered N-bromosuccinimide. After 2 hr of stirring, the chloroform was removed by distillation and the succinimide was removed by sublimation at 110° under vacuum to yield 2.34 g (100%) of crude tribromo chelate. This was purified by recrystallization from approximately 30 ml of xylene to yield 1.20 g (54% yield) of tris(N-methyl-5-bromosalicylaldiminato)cobalt(III), mp 279–281°, identical with an authentic sample,[20] mp 283–285° [λ_{max}, 396, 575 sh, 648 sh mμ (ϵ 8900, 355, $-cm^{-1}M^{-1}$), benzene, 25°]. The brominated chelate forms a 1:1 solvate with xylene, as evidenced by elemental, infrared, and nmr analysis, which was only slowly desolvated at 140° under vacuum.

Anal. Calcd for $C_{32}H_{31}Br_3CoN_3O_3$: C, 47.79; H, 3.88; N, 5.22; Co, 7.33. Found: C, 48.26; H, 4.18; N, 5.25; Co, 7.36.

A hexabromide was prepared by the above procedure using 1.54 g of unbrominated cobalt(III) complex and 3.6 g of N-bromosuccinimide. Isolation of the very insoluble product as above yielded 2.96 g of crude material and 2.24 g (71%) of pure tris(N-methyl-3,5-dibromosalicylaldiminato)cobalt(III) recrystallized from xylene and dried at 140° under vacuum. Under these conditions the solvent was removed only with great difficulty. The chelate also was found to be rather insoluble in most common solvents except at high temperatures, and the nmr spectrum of this chelate was obtained in a nitrobenzene solution. An authentic sample of this material was prepared from 3,5-dibromosalicylaldehyde by the method of West[21] and melted at 302–303° dec [λ_{max}, 395, 590, 654 sh mμ (ϵ 9400, 430, ... cm^{-1} benzene, 25°].

Anal. Calcd for $C_{24}H_{18}Br_6CoN_3O_3$: C, 30.84; H, 1.94; N, 4.50; Co, 6.30. Found: C, 31.39; H, 2.16; N, 4.60; M^{-1}) Co, 5.80.

Spectra.—The infrared spectra were obtained using the Nujol mull technique, sodium chloride plates, and a Beckman Model 10 grating instrument. The near-infrared spectra and the visible spectra were obtained using a Cary Model 14 spectrometer using benzene solutions or Nujol mulls mounted on filter paper. Nmr spectra were obtained using deuteriochloroform solutions with tetramethylsilane as an internal standard. All spectra were recorded using a Varian 60 Mc/sec fixed-frequency instrument with the downfield direction being considered as the negative direction. Melting points were recorded using a Mel-Temp apparatus.

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