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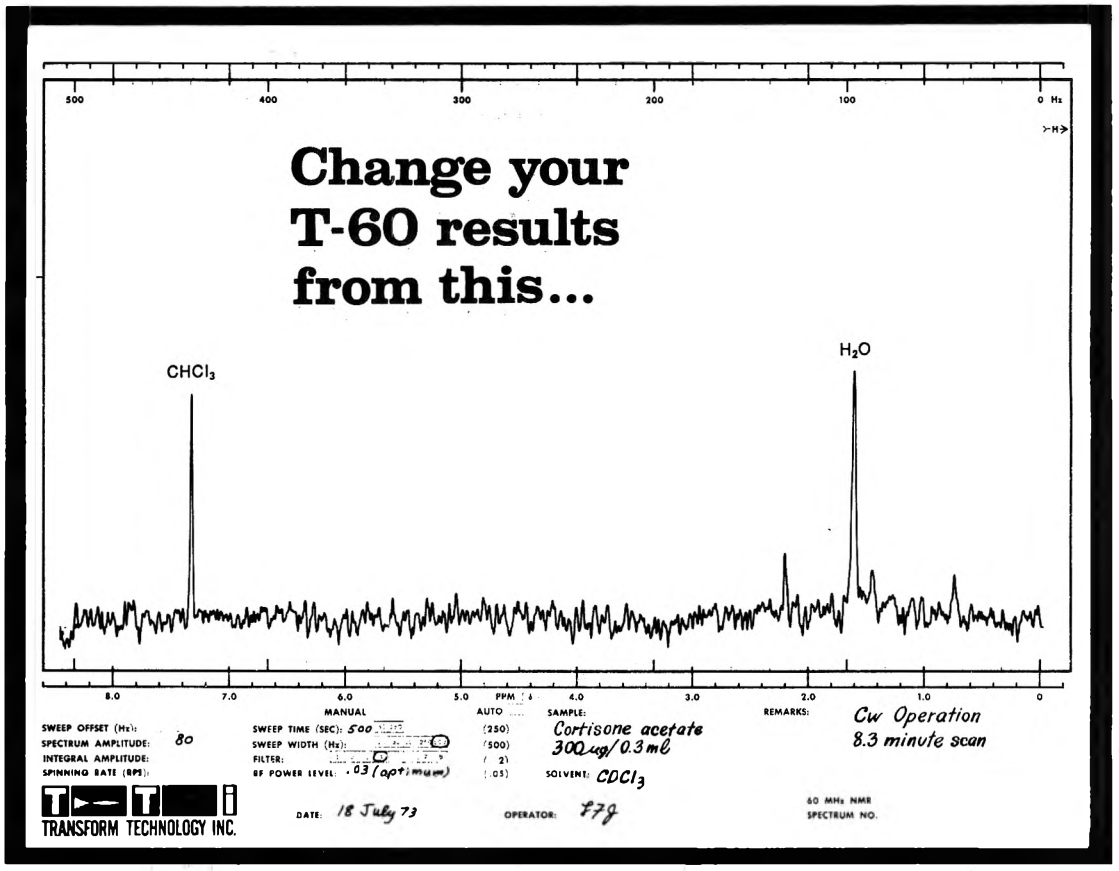
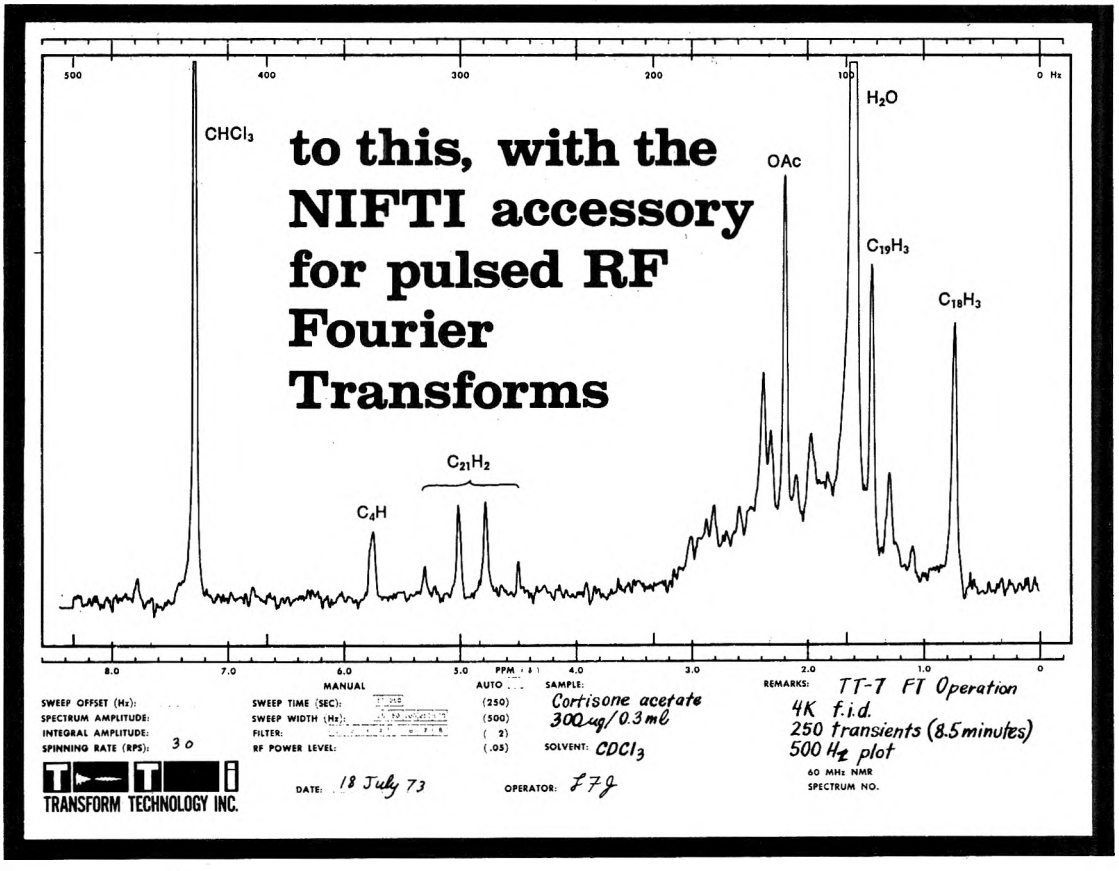
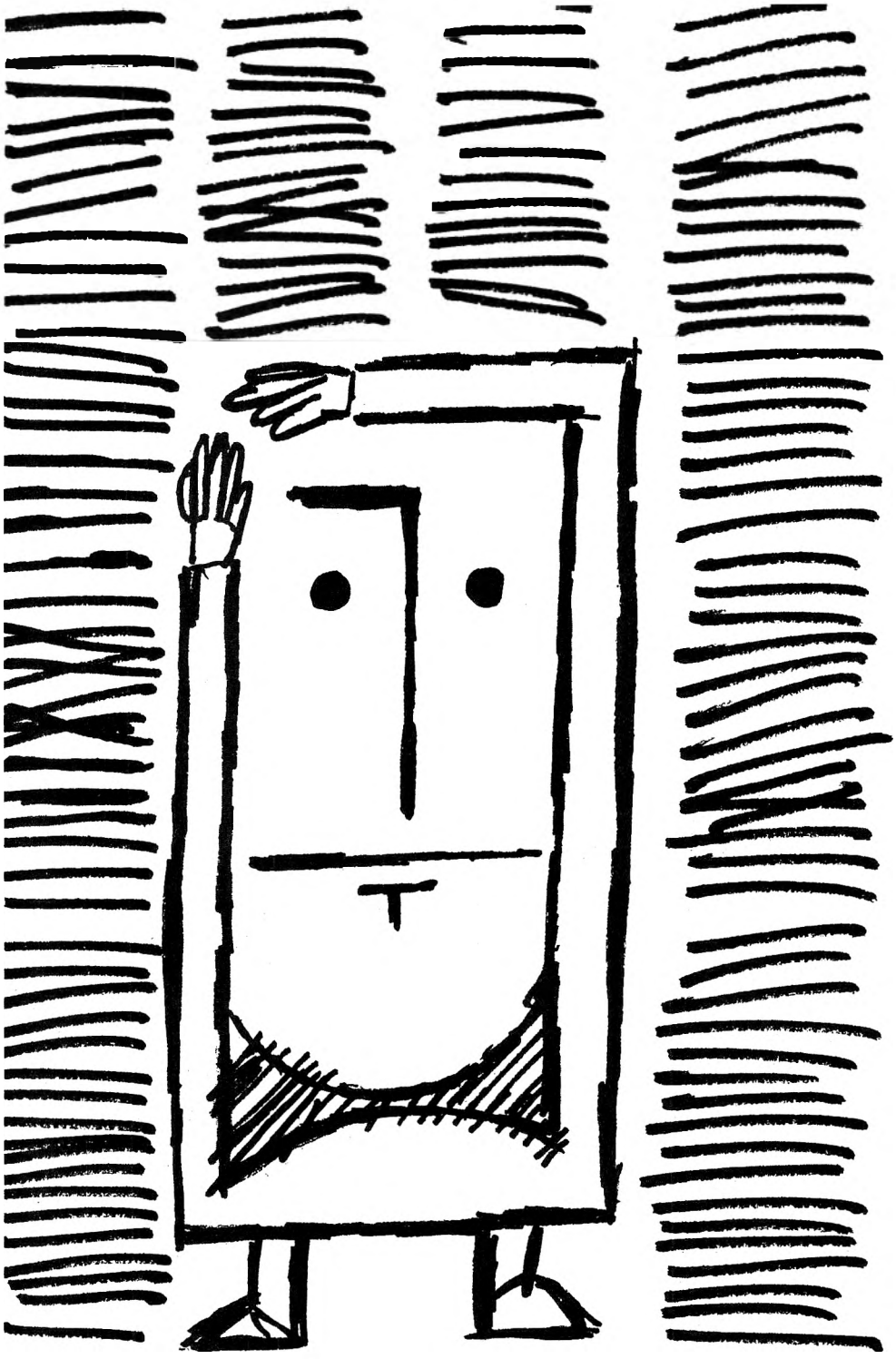




These two spectra were obtained in 500 seconds. One was run using conventional swept continuous wave (cw) techniques on a T-60, and the other was run in FT mode using the TT-7 FT accessory for the T-60. The sample was cortisone acetate (300 ug / 0.3 ml) in $CDCl_3$. This amounts to 2.5 x 10^{-3}M or 0.1%. The additional sensitivity obtained through the pulsed Fourier method is astonishing. The 500 sec cw scan only shows lines for the OAc and C_{18} methyl groups unambiguously. However, nearly the entire spectrum is clearly presented during 500 seconds of pulsed accumulation, since in the same time, 250 scans were summed. Note in particular that the C_4H line and the $C_{12}H_2$ quartet are not even suggested by the cw spectrum, while the pulsed FT spectrum shows them clearly.



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The Synthesis and Transformations of Some 3-Chloro- and 3-Nitroindolenines

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Received January 22, 1973

3-Substituted indole-2-carboxylic acid esters and amides are readily converted to the corresponding 3-chloroindolenines by reaction with *tert*-butyl hypochlorite. These compounds rearrange in protic solvents to oxindoles with migration of the ester or amide function into the 3 position. 3-Substituted 2-acetylindoles and indole-2-carboxylic acids are converted to the oxindoles with loss of the carbonyl function. The intermediate 2-alkoxyindoles may be isolated. Nitration of 3-substituted indole-2-carboxylates yields the corresponding 3-nitroindolenines. The structure of ethyl 5-chloro-3-nitro-3-phenyl-3*H*-indole-2-carboxylate was determined by X-ray analysis. Ethyl 3-nitroindolenine-2-carboxylates also undergo acid-catalyzed rearrangement to ethyl oxindolecarboxylates. Treatment of 2-acetyl-3-nitroindolenines with trifluoroacetic acid results in the formation of 2-nitroindoles.

The oxidative rearrangement of indoles to oxindoles during halogenation is by now a common reaction.[1,2] It has been demonstrated in the alkaloid field[3,4] that 3-haloindolenines are the key intermediates in this overall transformation. With few exceptions,[5,6] however, 3-chloroindolenines have seldom been properly characterized, and until recently[7] no simple analog was disclosed in the literature.

We have obtained crystalline 3-chloroindolenines of formula **2** (Scheme I) by treating indole derivatives of structure **1** with *tert*-butyl hypochlorite in aprotic solvents. These 3-chloroindolenines were found to be of limited stability and to convert exothermally and in high yields to oxindoles **3** in protic solvents such as alcohol. The structure of these compounds was derived from their spectroscopic data and confirmed by conversion of ethyl 3-phenyloxindole-3-carboxylate (**3a**) to the known 3-phenyloxindole **4**.

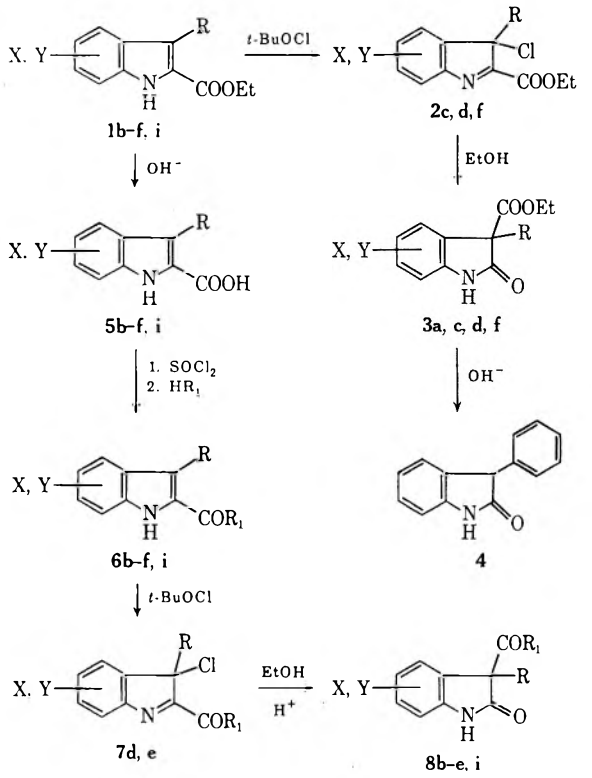
We have successfully extended this reaction to the indole-2-carboxamides **6**, which were prepared by standard methods *via* the indole-2-carboxylic acids **5**. Reaction of the indole-2-carboxamides with *tert*-butyl hypochlorite again produced the crystalline 3-chloroindolenines **7**. These compounds underwent the same transformation to the oxindoles **8** when subjected to protic solvents. The fact that even the primary amide **6d** rearranged in the same manner as the ester indicates that the carbonyl group migrates with its electrons. We believe that the mechanism of the reaction is best represented by the sequence of steps shown in Scheme II.

The protonated chlorindolenine A is assumed to be transformed to the carbonium ion C *via* a cyclic chloronium ion B. Migration of the carbonyl function with elimination of a proton leads to the imino chloride D, hydrolysis of which yields the oxindole **3**. Ethanolysis would convert the imino chloride to the oxindole **3** *via* the imino ether E. As illustrated by examples in Scheme III, the 2-acetylindole **9c** and the indole-2-carboxylic acids **5** undergo similar reactions. In both cases the carbonyl function was lost during the conversion of the 3-chloroindolenine to the oxindole. Thus refluxing 2-acetyl-3,5-dichloro-3-phenyl-3*H*-indole (**10**) in ethanol yielded 5-chloro-3-phenyloxindole (**12**). The intermediate 2-ethoxyindole **11** could be isolated under milder reaction conditions. According to the mechanism proposed in Scheme II, the 2-ethoxyindole would originate from deacetylation of the imino ether E. This would require migration of the carbonyl function prior to deacetylation. Possible deacetylation of the carbonium ion C was excluded by showing that the 2-chloroindole **13**, which would result from this deacetylation, does not convert to the 2-ethoxyindole **11** under reaction conditions. The 3-chloroindolenines derived from the indole-2-carboxylic acids **5c** and **5i** were not isolated but directly treated with ethanol and methanol, respectively, to afford **11** and the 2-methoxyindole **15**.

Reaction of the 3-chloroindolenine **10** with trifluoroacetic acid produced mainly a mixture of compounds **13** and **14** (separated by chromatography). For comparison the 2,5-dichloroindole **13** was prepared

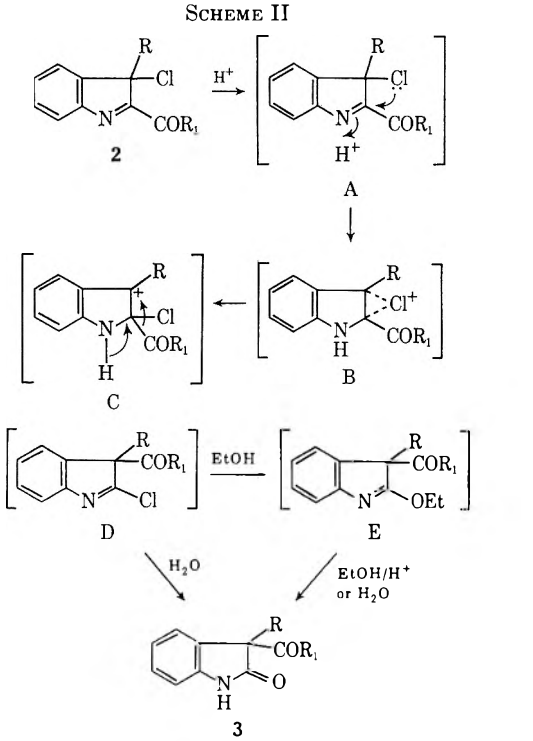
(1) J. M. Muchowski, *Can. J. Chem.*, **48**, 422 (1970).
(2) R. M. Acheson, R. W. Snaith, and J. M. Vernon, *J. Chem. Soc.*, 3229 (1964).
(3) N. Finch and W. I. Taylor, *J. Amer. Chem. Soc.*, **84**, 3871 (1962).
(4) K. V. Lichman, *J. Chem. Soc.*, 2539 (1971).
(5) N. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **10**, 1414 (1956).
(6) H. Finnes and J. Shavel, Jr., *J. Org. Chem.*, **31**, 1765 (1966).
(7) While this manuscript was in preparation the synthesis and transformations of 3-chloro-2,3-dimethylindolenine have been reported by P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron*, **28**, 2749 (1972).

SCHEME I



Compd	X, Y	R	R_1
a		C_6H_5	
b		CH_3	1-Pyrrolidino
c	5-Cl	C_6H_5	$N(Et)_2$
d	5-Cl	2-FC_6H_4	NH_2
e	5-Cl	2-FC_6H_4	NHEt
f	5-Cl	CH_3	1-Aziridino
g	5,7-di-Cl	C_6H_5	
h	4,7-di-Cl	C_6H_5	
i	6,7-di-Cl	C_6H_5	1-Morpholino
k	5,7-di-CH_3	C_6H_5	

SCHEME II



by heating the oxindole **12** with phosphorus oxychloride. Acetylation of **13** with acetic anhydride in boiling pyridine yielded **14** which in turn was hydrolyzed with alkali to give **13**. Formation of compounds **13** and **14** may follow the same mechanistic scheme. In this case nothing speaks against deacetylation of the carbonium ion C leading to the 2-chloroindole **13** and the mixed anhydride of trifluoroacetic and acetic acids, which is probably responsible for the formation of the acetyl derivative **14**.

To further explore the limitations of this reaction we prepared the vinylogous ester **17** as outlined in Scheme IV. The indole-2-carboxylic acid **5f** was converted to the aziridide **6f**, the reduction of which with lithium aluminum hydride yielded the aldehyde **16**. Treatment of **16** with ethyl diethylphosphonoacetate and base led to **17**. The crystalline 3-chloroindolenine **18** was readily formed but failed to undergo the rearrangement to the oxindole. Two products were isolated instead. Based on spectroscopic data we have assigned structure **19** to the major product and structure **20** to the minor component. Again, a cyclic chloronium ion such as G may be postulated. Removal of a proton from the α position of G leads to **20**; addition of ethoxide results in formation of **19**.

Analogous to the chlorination, nitration of unprotonated 2,3-disubstituted indoles has been thoroughly studied[8,9] but no 3-nitroindolenines have been described.

We obtained the crystalline 3-nitroindolenines **21** and **23** (Scheme V) by treating the 2,3-disubstituted indoles **1** and **9** with fuming nitric acid at low temperatures. Since the alternate 1-nitroindole structure **22** could not be excluded based on spectral and chemical data, the 3-nitroindolenine structure was confirmed by the single-crystal X-ray diffraction of ethyl 5-chloro-3-nitro-3-phenyl-3*H*-indole-2-carboxylate (**21c**).

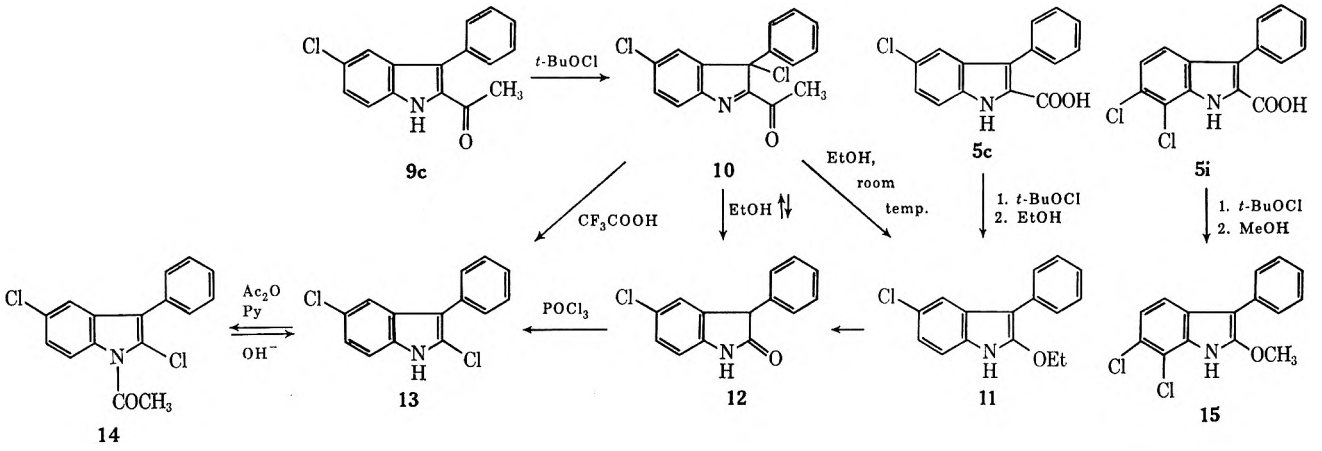
The preparation of 3-nitroindolenines seems to be limited to indoles which are not susceptible to electrophilic attack in the benzene moiety. For example, we were unsuccessful in preparing 5-methoxy-3-nitroindolenines. It was found that 3-nitroindolenines are more stable than the corresponding 3-chloroindolenines. In analogy to the 3-chloroindolenines, ethyl 3-nitro-3-phenyl-3*H*-indole-2-carboxylates **21** were found to undergo an acid-catalyzed rearrangement to the oxindoles **3**. The reaction was slower and less clean than with the 3-chloroindolenines and the yields were inferior. Mechanistically, the reaction can be visualized as proceeding *via* a cyclic nitronium ion analogous to that proposed by Berti[9] and his coworkers. In the hydrogen chloride catalyzed reaction, however, the possibility of formation of the intermediate 3-chloroindolenines cannot be ruled out.

Treatment of the 2-acetyl-3-nitroindolenines **23** with trifluoroacetic acid resulted in a clean conversion to the 2-nitroindoles **24**. Berti and coworkers[9] have described the only 2-nitroindole that we could find in the literature. These authors treated 3-methylindole with benzoyl nitrate and obtained 3-methyl-2-nitroindole in 4.5% yield. The spectroscopic properties of 5-chloro-3-methyl-2-nitroindole (**24f**) are in agreement with the data reported by Berti and coworkers for 3-methyl-2-nitroindole. The formation of 2-nitroindoles from 2-acetyl-3-nitroindolenines is mechanistically difficult to explain. If a cyclic nitronium ion would be involved in this reaction we would

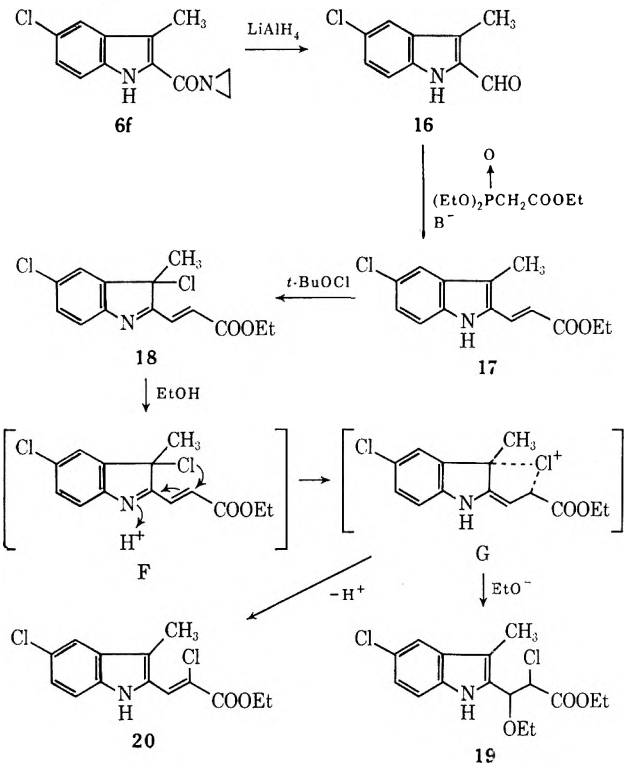
(8) W. E. Noland, K. R. Rush, and L. R. Smith, *J. Org. Chem.*, **31**, 65 (1966); W. E. Noland and K. R. Rush, *ibid.*, **31**, 70, (1966).

(9) G. Berti, A. DaSettimo, and E. Nannipieri, *J. Chem. Soc.*, 2145 (1968).

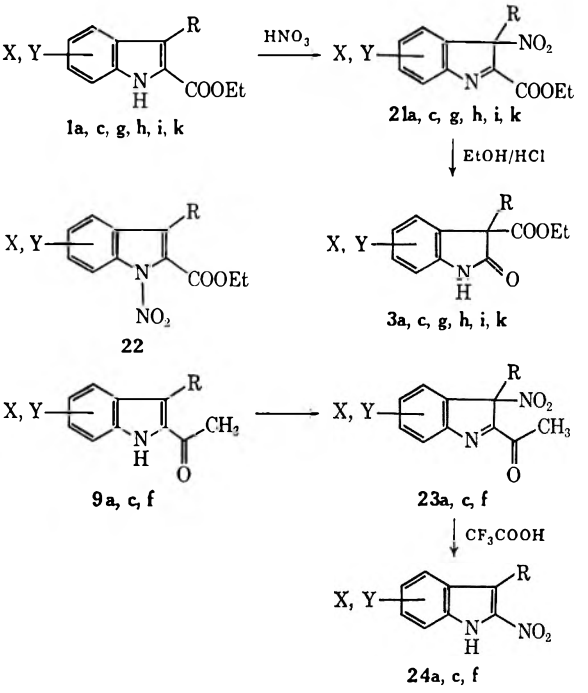
SCHEME III



SCHEME IV



SCHEME V



obtain the indole-2-nitrite rather than the 2-nitroindole. The 1,2 migration of a nitro group is more likely the result of dissociation and renitration together with displacement of the acetyl group. Nitration of 5-nitro-3-formylindole with replacement of the formyl group has been reported by Noland and Rush.[8]

Crystallography.—Crystals of **21c** are monoclinic, space group $P2_1/c$. The crystal data are a = 7.746 (3), b = 15.053 (5), c = 13.898 (5) Å, β = 100.23 (2)°, Z = 4, d_{obsd} = 1.44, d_{calcd} = 1.435 g cm^{-3}, μ (Cu K$_\alpha$) = 23.5 cm^{-1}. Despite the fact that **21c** crystallizes from CH_2Cl_2–Et_2O as elongated prisms with well-defined faces, many of the crystals failed to extinguish properly under crossed polarizing filters. Most crystals which were examined with a polarizing microscope could be considered as composed of two parts, one which extinguished properly and another which never extinguished. The boundary between these two parts was always sharp and ran parallel to the length of the crystal. No difference could be detected between Weissenberg photographs of crystals for which the whole crystal extinguished and those for which only one part of the crystal extinguished. The crystals used for data collection were those for which almost the entire crystal extinguished under crossed polaroids.

The intensity data were measured on a Hilger-Watts Model Y290 four-circle diffractometer by θ–2θ scans. Nickel-filtered Cu K$_\alpha$ radiation and pulse height discrimination were used. The crystals deteriorated slowly upon exposure to X-rays (25% decrease in the intensity of the three standard reflections over a 3-day period). Intensity data were collected from two crystals, one approximately 0.09 × 0.09 × 0.45 mm (used for $2\theta < 107°$) and the other 0.12 × 0.14 × 0.35 mm (used for $85 < 2\theta < 127°$). The intensity data were corrected for crystal deterioration, then placed on a common scale; no absorption correction was made.

The structure was solved by standard Patterson and Fourier methods. The hydrogen atoms were located from a difference Fourier calculated after partial refinement of the structure. The final refinement was by block-diagonal least squares with the matrix partitioned into five blocks. Anisotropic thermal parameters were used for all atoms except the hydrogens; the hydrogen atom parameters were not refined.

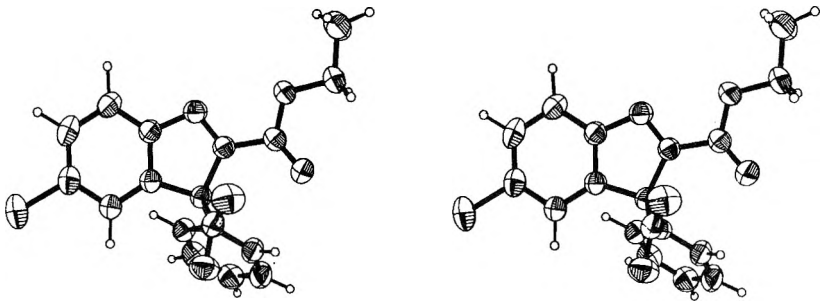


Figure 1.—Stereodrawing of **21c** showing its conformation in the solid state. The ellipsoids represent the thermal motions of each atom at the 50% probability level. The hydrogen atoms are represented as spheres of an arbitrary size.

The quantity minimized was

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

where $w = 1/(8.5 + |F_o| + 0.013\ |F_o|^2)$. Standard scattering curves were used for Cl, O, N, C,[10] and H.[11] The Cl curve was corrected for the real and imaginary parts of the anomalous scattering.[12] The refinement was stopped when the shifts of all parameters were less than one fifth of the corresponding standard deviations. The difference Fourier based on the final parameters has no features >0.2 eÅ^{-3} in magnitude.

$$\text{final } R = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.041$$

The bond lengths and angles in **11b** are in agreement with the expected values; the N_1–C_2 distance is 1.287 (5) Å. The conformation of the molecule is shown in Figure 1. The phenyl ring of the indolenine system is planar to within 0.006 Å. The indolenine nitrogen and the 2 and 3 position carbon atoms [C(2) and C(3)] are displaced 0.02, 0.06, and −0.02 Å, respectively, from the plane of the indolenine phenyl ring. The nitrogen of the 3-nitro group is 0.03 Å out of the plane of C(3) and the two oxygens. The displacement is toward the carboxyl oxygen (N···O distance, 3.20 Å). The final atomic parameters and the observed and calculated structure factors appear in the microfilm in edition of this journal.[13]

Experimental Section

Melting points were determined in a capillary melting point apparatus. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer; nmr spectra were recorded with a Varian A-60 or Varian T-60 instrument. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70–325 mesh) was used for chromatography.

Ethyl indole-2-carboxylates (1) were prepared by the Japp–Klingemann reaction[14] following the procedure described by Hughes, *et al.*[15]

Ethyl 5,7-dichloro-3-phenylindole-2-carboxylate (1g) had mp 148–150°; ir ($CHCl_3$) 1705, 1740 cm^{-1} (COOEt); uv λ_{max} 238–239 mμ (ε 39,000), 298–299 (14,600), sh 320 (7300).

Anal. Calcd for $C_{17}H_{13}Cl_2NO_2$: C, 61.00; H, 3.92; N, 4.19. Found: C, 60.99; H, 3.86; N, 4.03.

Ethyl 4,7-dichloro-3-phenylindole-2-carboxylate (1h) had mp 130–132°; ir ($CHCl_3$) 1705, 1740 cm^{-1} (COOEt); uv λ_{max} 241 mμ (ε 38,200), 296–297 (16,300), 320 (8250).

Anal. Calcd for $C_{17}H_{13}Cl_2NO_2$: C, 61.00; H, 3.92; N, 4.19. Found: C, 60.49; H, 3.77; N, 4.09.

Ethyl 6,7-dichloro-3-phenylindole-2-carboxylate (1i) had mp 154–155°; ir ($CHCl_3$) 1700, 1730 cm^{-1}; uv λ_{max} 241 mμ (ε 38,600), 303 (18,000), infl 325 (8500).

Anal. Calcd for $C_{17}H_{13}Cl_2NO_2$: C, 61.00; H, 3.92; N, 4.19. Found: C, 61.11; H, 3.91; N, 4.18.

Ethyl 5,7-dimethyl-3-phenylindole-2-carboxylate (1k) had mp 126–128°; ir ($CHCl_3$) 1690, 1710 cm^{-1}; uv λ_{max} 225 mμ (ε 25,150), 242 (26,100), 302 (18,400), infl 335 (6800).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.50; H, 6.34; N, 4.62.

Indole-2-carboxylic acids **5** were accessible by alkaline hydrolysis of the corresponding ester according to the standard procedure.

5-Chloro-3-methylindole-2-carboxylic acid (5f) had mp 238–240° dec.

Anal. Calcd for $C_{10}H_8ClNO_2$: C, 57.29; H, 3.84; N, 6.68. Found: C, 57.37; H, 3.80; N, 6.51.

6,7-Dichloro-3-phenylindole-2-carboxylic acid (5i) had mp 219–221°.

Anal. Calcd for $C_{15}H_9Cl_2NO_2$: C, 58.85; H, 2.96; N, 4.58. Found: C, 58.77; H, 3.11; N, 4.32.

Indole-2-carboxamides were obtained by converting the indole-2-carboxylic acids with thionyl chloride or phosphorus pentachloride to the acid chlorides which were directly treated with the amines.

5-Chloro-3-(2-fluorophenyl)indole-2-carboxamide (6d).[14]—A mixture of 14.5 g (0.05 mol) of 5-chloro-3-(2-fluorophenyl)indole-2-carboxylic acid (**5d**),[14] 12 g of phosphorus pentachloride, and 400 ml of methylene chloride was stirred at room temperature for 30 min. Concentrated aqueous ammonia was added with ice cooling until the aqueous phase was strongly alkaline. The precipitated crystals were collected and recrystallized from methanol to yield 10.2 g of product, mp 209–212°. From the evaporated methylene chloride phase and the mother liquor, another 2 g of product was obtained, yield 12.2 g (84%).

1-(5-Chloro-3-methylindole-2-carbonyl)aziridine (6f).—A mixture of 42 g (0.2 mol) of 5-chloro-3-methylindole-2-carboxylic acid (**5f**), 100 ml of thionyl chloride, and 200 ml of methylene chloride was refluxed for 16 hr. The solvent and excess thionyl chloride were evaporated under reduced pressure, at the end azeotropically with benzene. The residue was dissolved in tetrahydrofuran and added to a solution of 25 ml of aziridine in 200 ml of methylene chloride cooled to 0°.

A 150-ml portion of 10% aqueous sodium carbonate solution was added at 0° and the two-phase mixture was stirred for 2 hr at room temperature. The methylene chloride layer was separated, dried over sodium sulfate, and evaporated. Crystallization of the residue from methylene chloride–hexane yielded 38 g (81%) of product, mp 140–142°.

The analytical sample was recrystallized from methylene chloride–ether: mp 145–146°; uv λ_{max} 235 mμ (ε 21,400), 310 (21,000).

Anal. Calcd for $C_{12}H_{11}ClN_2O$: C, 61.42; H, 4.72; N, 11.93. Found: C, 61.43; H, 4.88; N, 12.09.

The following amides were prepared in the same way.

5-Chloro-*N*,*N*-diethyl-3-phenylindole-2-carboxamide (6c) had mp 195–198°; uv λ_{max} 226 mμ (ε 35,000), sh 265 (11,050), 293–297 (11,400).

Anal. Calcd for $C_{19}H_{19}ClN_2O$: C, 69.83; H, 5.86; N, 8.57. Found: C, 69.69; H, 5.89; N, 8.61.

5-Chloro-*N*-ethyl-3-(2-fluorophenyl)indole-2-carboxamide (6e) had mp 248–250°; uv λ_{max} 233 mμ (ε 35,000), 300 (16,000).

Anal. Calcd for $C_{17}H_{14}ClFN_2O$: C, 64.40; H, 4.45; N, 8.84. Found: C, 64.40; H, 4.15; N, 8.78.

(10) D. T. Cromer and J. T. Waber, *Acta Crystallogr.*, **18**, 104 (1965).
(11) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).
(12) D. T. Cromer, *Acta Crystallogr.*, **18**, 17 (1965).
(13) See paragraph at end of paper regarding supplementary material.
(14) R. R. Phillips, *Org. React.*, **10**, 143 (1959).
(15) G. K. Hughes, *et al.*, *J. Proc. Roy. Soc. N. S. W.*, **71**, 475 (1959).

1-(3-Methylindole-2-carbonyl)pyrrolidine (6b) had mp 232–234°; uv λ_{max} 222 mμ (ε 32,200), infl 242 (12,000), 293 (14,400).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.84; H, 7.30; N, 12.28.

1-(6,7-Dichloro-3-phenylindole-2-carbonyl)morpholine (6i) had mp 129–135°; uv λ_{max} 233 mμ (ε 32,500), 298 (11,500).

Anal. Calcd for $C_{19}H_{16}Cl_2N_2O_2$: C, 60.81; H, 4.30; N, 7.46. Found: C, 60.79; H, 4.44; N, 7.32.

2-Acetylindoles **9c** and **9f** were prepared by the modified Japp–Klingemann reaction following a procedure described by Manske, Perkin, and Robinson.[16]

2-Acetyl-5-chloro-3-phenylindole (9c) had mp 151–153°; ir ($CHCl_3$) 1650 cm^{-1}; uv λ sh 232 mμ (ε 21,000), max 244 (21,900), 313 (19,250), infl 345 (6600).

Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.49; N, 5.19. Found: C, 71.48; H, 4.55; N, 5.18.

2-Acetyl-5-chloro-3-methylindole (9f) had mp 200–202°; ir ($CHCl_3$) 1655 cm^{-1}; uv λ_{max} 238 mμ (ε 9400), 312 (20,450).

Anal. Calcd for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.53; H, 4.74; N, 6.79.

3-Chloroindolenines (**10**) were obtained by reaction of the indoles with *tert*-butyl hypochlorite in methylene chloride or tetrahydrofuran. The reactions were followed by thin layer chromatography and were found to be in general complete within 15 min to a few hours at room temperature.

2-Acetyl-3,5-dichloro-3-phenyl-3*H*-indole (10).—A 15-ml portion of *tert*-butyl hypochlorite (14.3 g, 0.133 mol) was added to a solution of 27 g (0.1 mol) of 2-acetyl-5-chloro-3-phenylindole (**9c**) in 300 ml of methylene chloride. After sitting for 30 min at room temperature the solvent was removed under reduced pressure. The residue crystallized from methylene chloride–hexane to yield 27.5 g (90%) of product: mp 145–148° dec; nmr ($CDCl_3$) δ 2.6 (s, 3, $COCH_3$), 7.33 (s, 5, C_6H_5), 7.8 (d, 1, J = 8 Hz, C_7H), 7.25–7.7 (m, 2, C_4H and C_6H); uv (CH_2Cl_2) λ_{max} 251 mμ (ε 15,400) 322 (7100); ir ($CHCl_3$) 1700 cm^{-1} (CO).

Anal. Calcd for $C_{16}H_{11}Cl_2NO$: C, 63.18; H, 3.65; N, 4.60. Found: C, 63.30; H, 3.55; N, 4.60.

***N*-Ethyl-3,5-dichloro-3-(2-fluorophenyl)-3*H*-indole-2-carboxamide (7e)**.—A 1.6-g (5 mmol) portion of *N*-ethyl-5-chloro-3-(2-fluorophenyl)indole-2-carboxamide (**6e**) was dissolved in 100 ml of tetrahydrofuran by warming. *tert*-Butyl hypochlorite (2 ml, 17.5 mmol) was added to the warm solution. After sitting for 10 min, the solvent was removed under reduced pressure and the residue was crystallized from methylene chloride–hexane to yield 1.6 g (91%) of product: mp 160–162°; nmr ($CDCl_3$) δ 1.2 (t, 3, J = 7 Hz, CH_3), 3.42 (quintuplet, 2, J = 7 Hz, CH_2), 6.6–8.2 (m, 8, NH and 7 aromatic H); uv λ_{max} 243 mμ (ε 19,900), infl 269 (5020), 320 (6980); ir ($CHCl_3$) 1680 cm^{-1} (CO).

Anal. Calcd for $C_{17}H_{13}Cl_2FN_2O$: C, 58.14; H, 3.73; N, 7.98. Found: C, 58.17; H, 3.66; N, 7.90.

As above the following were prepred.

Ethyl 3,5-dichloro-3-phenyl-3*H*-indole-2-carboxylate (2c) had mp 110–113°, crystallized from methylene chloride–hexane; uv (CH_2Cl_2) λ_{max} 246 mμ (ε 17,000), 325 (6420); ir ($CHCl_3$) 1725 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.3 (t, 3, J = 7 Hz, CH_3), 4.36 (q, 2, J = 7 Hz, CH_2), 7.37 (s, 5, C_6H_5), 7.83 (d, 1, J = 8 Hz, C_7H), 7.25–7.7 (m, 2, C_4 and C_6 H).

Anal. Calcd for $C_{17}H_{13}Cl_2NO_2$: C, 61.10; H, 3.92; N, 4.19. Found: C, 61.46; H, 4.11; N, 4.15.

Ethyl 3,5-dichloro-3-(2-fluorophenyl)-3*H*-indole-2-carboxylate (2d) had mp 120–123°, crystallized from methylene chloride–hexane; uv (CH_2Cl_2) λ_{max} 245 mμ (ε 18,150) 322 (6580); ir ($CHCl_3$) 1735 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.32 (t, 3, J = 7 Hz, CH_3), 4.4 (q, 2, J = 7 Hz, CH_2), 7.8 (d, 1, J = 8 Hz, C_7 H), 6.7–8.5 (m, 6, aromatic protons).

Anal. Calcd for $C_{17}H_{12}Cl_2FNO_2$: C, 57.98; H, 3.43; N, 3.97. Found: C, 58.08; H, 3.27; N, 3.93.

3,5-Dichloro-3-(2-fluorophenyl)-3*H*-indole-2-carboxamide (7d) had mp 186–188° dec, crystallized from tetrahydrofuran–hexane; uv λ_{max} 242 mμ (ε 18,800), 318 (6500); ir (KBr) 1680 cm^{-1} (CO).

Anal. Calcd for $C_{15}H_9Cl_2FN_2O$: C, 55.75; H, 2.81; N, 8.67. Found: C, 55.79; H, 2.72; N, 8.59.

***trans*-Ethyl 3-(3,5-dichloro-3-methyl-3*H*-indolyl)propenoate (18)** was obtained in 90% yield by treating 2.65 g (10 mmol) of *trans*-ethyl 3-(5-chloro-3-methyl-2-indolyl)propenoate (**17**) in 50 ml of methylene chloride with 2.5 ml (22 mmol) of *tert*-butyl hypochlorite for 3 hr at room temperature: mp 100–102°, crystallized from ether–hexane; uv λ_{max} 271 mμ (ε 12,800); ir ($CHCl_3$) 1720 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.37 (t, 3, J = 7 Hz, CH_3), 1.97 (s, 3, CH_3), 4.33 (q, 2, J = 7 Hz, CH_2), 7.02 (d, 1, J = 17 Hz), and 7.64 (d, 1, J = 17 Hz, olefinic H), 7.2–7.7 (m, 3, aromatic H).

Anal. Calcd for $C_{14}H_{13}Cl_2NO_2$: C, 56.39; H, 4.39; N, 4.70. Found: C, 56.39; H, 4.33; N, 4.67.

5-Chloro-3-methylindole-2-carboxaldehyde (16).—A 23.5-g (0.1 mol) portion of 1-(5-chloro-3-methylindole-2-carbonyl)aziridine (**6f**) was added in portions at 0° to a suspension of 5.6 g (0.14 mol) of lithium aluminum hydride in 200 ml of ether. The mixture was stirred at 0° for 1 hr and at room temperature for another 1 hr. The hydride was hydrolyzed by addition of 30 ml of water. The inorganic material was filtered and washed well with tetrahydrofuran. The filtrate was concentrated and the residue was slurried with ether. The collected solid was recrystallized from tetrahydrofuran–ethanol to yield 8.5 g (44%) of product, mp 248–250°. The analytical sample was recrystallized from methylene chloride–methanol: mp 250–252°; uv λ_{max} 238 mμ (ε 18,800), 314 (23,150); ir (KBr) 1640 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; N, 7.24. Found: C, 62.17; H, 4.24; N, 7.08.

***trans*-Ethyl 3-(5-Chloro-3-methyl-2-indolyl)propenoate (17)**.—A 6-g (53 mmol) portion of potassium *tert*-butoxide was added to a solution of 10.5 g (52.5 mmol) of ethyl diethylphosphonoacetate in 50 ml of tetrahydrofuran. After stirring for 15 min under nitrogen, a solution of 6 g (21 mmol) of 5-chloro-3-methylindole-2-carboxaldehyde (**16**) in 300 ml of tetrahydrofuran was added. The mixture was stirred for 2 hr at room temperature and partitioned between 200 ml of methylene chloride and 300 ml of hexane and water. The organic layer was separated, washed with water, dried, and evaporated. Crystallization of the residue from ethanol yielded 6.1 g (75%) of product, mp 178–183°. The analytical sample was recrystallized from ethanol: mp 183–184°; uv λ_{max} 239 mμ (ε 12,400), 254 (11,100), 345 (32,700); ir ($CHCl_3$) 1700 cm^{-1} (CO); nmr (DMSO) δ 1.29 (t, 3, J = 7 Hz, CH_3), 2.32 (s, 3, CH_3), 4.22 (q, 2, J = 7 Hz, CH_2), 6.52 (d, 1, J = 16 Hz, α proton), 7.2 (q, 1, J_{AB} = 8 Hz, J_{AX} = 2 Hz, C_6 H), 7.4 (d, 1, J_{AB} = 8 Hz, C_7 H), 7.64 (d, 1, J_{AX} = 2 Hz, C_4 H), 7.7 (d, 1, J = 16 Hz, β proton), 11.45 (broad s, 1, NH).

Anal. Calcd for $C_{14}H_{14}ClNO_2$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.82; H, 5.37; N, 5.03.

Ethyl 5-Chloro-3-nitro-3-phenyl-3*H*-indole-2-carboxylate (21c).—A 10-ml portion of fuming nitric acid was added to a solution of 15 g of ethyl 5-chloro-3-phenylindole-2-carboxylate[17] in 300 ml of methylene chloride cooled to −50°. The temperature was allowed to reach −30° within 30 min. A 150-ml portion of 10% aqueous sodium carbonate solution was added with stirring. The methylene chloride layer was separated, washed with sodium carbonate solution and water, dried over sodium sulfate, and concentrated below 30°. The product crystallized upon addition of ether, yield 13.7 g (79%), mp 117–120° dec.

The analytical sample was recrystallized from methylene chloride–hexane: mp 120–124° dec; uv λ_{max} 238 mμ (ε 15,560), 321 (6800); ir (KBr) 1730 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.33 (t, 3, J = 7 Hz, CH_3), 4.36 (q, 2, J = 7 Hz, CH_2), 7–7.7 (m, 7, aromatic H), 7.82 (d, 1, J = 8.5 Hz, C_7 H).

Anal. Calcd for $C_{17}H_{13}ClN_2O_4$: C, 59.23; H, 3.80; N, 8.13. Found: C, 59.41; H, 3.90; N, 8.13.

Ethyl 3-nitro-3-phenyl-3*H*-indole-2-carboxylate (21a) was obtained in 60% yield by treating 26.5 g (0.1 mol) of ethyl 3-phenylindole-2-carboxylate[15] in 300 ml of methylene chloride with 20 ml of fuming nitric acid at −50 to −38°: mp 79–81°, crystallized from ether–hexane; uv λ_{max} 233 mμ (ε 16,380), 311 (6020); ir (KBr) 1725 cm^{-1} (CO).

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.85; H, 4.55; N, 8.92.

Ethyl 4,7-Dichloro-3-nitro-3-phenyl-3*H*-indole-2-carboxylate (21h).—A 17-g (0.05 mol) portion of ethyl 4,7-dichloro-3-phenylindole-2-carboxylate (**1h**) in 300 ml of methylene chloride was treated at −10 to 18° with 10 ml of fuming nitric acid to yield 14.2 g (75%) of product with mp 124–126° after recrystallization from acetone–ethanol: uv λ_{max} 240 mμ (ε 13,500), 294 (4900), 327 (4750); ir ($CHCl_3$) 1740 cm^{-1} (CO).

Anal. Calcd for $C_{17}H_{12}Cl_2N_2O_4$: C, 53.85; H, 3.19; N, 7.39. Found: C, 53.81; H, 3.46; N, 7.44.

Ethyl 5,7-Dichloro-3-nitro-3-phenyl-3*H*-indole-2-carboxylate

(16) R. H. F. Manske, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, 1 (1927).

(17) H. Yamamoto, *et al.*, *Chem. Ber.*, **101**, 4245 (1968).

(21g).—Reaction of 17 g (0.05 mol) of ethyl 5,7-dichloro-3-phenylindole-2-carboxylate (1g) in 300 ml of methylene chloride with 10 ml of nitric acid at −10 to 5° yielded after two recrystallizations from methylene chloride–ethanol 6 g (31.5%) of product: mp 107–109°; uv λ_{max} 244 mμ (ε 13,620), 323 (6720); ir ($CHCl_3$) 1750 cm^{-1} (CO).

Anal. Calcd for $C_{17}H_{12}Cl_2N_2O_4$: C, 53.85; H, 3.19; N, 7.39. Found: C, 53.76; H, 3.36; N, 7.28.

Ethyl 6,7-dichloro-3-nitro-3-phenyl-3*H*-indole-2-carboxylate (21i) was obtained in 71% yield by reaction of 17 g (0.05 mol) of 6,7-dichloro-3-phenylindole-2-carboxylate (1i) in 400 ml of methylene chloride with 10 ml of nitric acid at −20 to 0°: mp 109–112°, crystallized from acetone–ethanol; uv λ_{max} 242 mμ (ε 17,700), 309 (6000); ir ($CHCl_3$) 1740 cm^{-1} (CO).

Anal. Calcd for $C_{17}H_{12}Cl_2N_2O_4$: C, 53.85; H, 3.19; N, 7.39. Found: C, 53.67; H, 3.38; N, 7.32.

Ethyl 5,7-Dimethyl-3-nitro-3-phenyl-3*H*-indole-2-carboxylate (21k).—Treating 14.7 g (0.05 mol) of ethyl 5,7-dimethyl-3-phenylindole-2-carboxylate (1k) in 300 ml of CH_2Cl_2 with 10 ml nitric acid at −60 to −50° for 5 min yielded a mixture of mainly two compounds. By crystallization from ether the by-product crystallized. Crystallization of the mother liquor from ethanol yielded 8.1 g (46%) of product, which was recrystallized from acetone–ethanol: mp 119–121°; uv λ_{max} 245 mμ (ε 14,400), 338 (7250); ir ($CHCl_3$) 1730 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.30 (t, 3, J = 7 Hz, CH_3), 2.36 (s, 3, CH_3), 2.63 (s, 3, CH_3), 4.33 (q, 2, J = 7 Hz, CH_2), 7–7.6 (m, 7, aromatic H).

Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.73; H, 5.40; N, 8.27.

2-Acetyl-3-nitro-3-phenyl-3*H*-indole (23a).—Reaction of 23.5 g (0.1 mol) of 2-acetyl-3-phenylindole[16] in 400 ml of methylene chloride with 20 ml of nitric acid at −50 to −25° (15 min) yielded 11.6 g (41%) of product, crystallized from ethanol: mp 122–124° dec; uv λ_{max} 235 mμ (ε 12,580), 315 (6480); ir ($CHCl_3$) 1700 cm^{-1} (CO); nmr ($CDCl_3$) δ 2.6 (s, 3, CH_3), 7–8 (m, 9, aromatic H).

Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.54; H, 4.32; N, 10.00. Found: C, 68.75; H, 4.19; N, 9.93.

2-Acetyl-5-chloro-3-nitro-3-phenyl-3*H*-indole (23c) was obtained in 38% yield by treating 27 g (0.1 mol) of 2-acetyl-5-chloro-3-phenylindole (9c) in 500 ml of methylene chloride with 20 ml of nitric acid at −30 to −5° for 15 min: mp 124–128° dec, crystallized from acetone–ethanol; uv λ_{max} 241 mμ (ε 13,400), 317 (7500); ir ($CHCl_3$) 1700 cm^{-1} (CO); nmr ($CDCl_3$) δ 2.6 (s, 3, CH_3), 7–8 (m, 8, aromatic H).

Anal. Calcd for $C_{16}H_{11}ClN_2O_3$: C, 61.06; H, 3.52; N, 8.90. Found: C, 60.93; H, 3.45; N, 9.13.

2-Acetyl-5-chloro-3-methyl-3-nitro-3*H*-indole (23f).—A 20.7-g (0.1 mol) portion of 2-acetyl-5-chloro-3-methylindole (9f) dissolved in 500 ml of methylene chloride was treated with 20 ml of fuming nitric acid at −30 to −5°. Crystallization from ether–ethanol yielded 10.2 g (40%) of product which was recrystallized twice from ether–ethanol: mp 93–94°; uv λ_{max} 240 mμ (ε 12,100), 324 (9140); ir ($CHCl_3$) 1690 cm^{-1} (CO); nmr ($CDCl_3$) δ 2.08 (s, 3, CH_3), 2.67 (s, 3, $COCH_3$), 7.3–7.7 (m, 3, aromatic H).

Anal. Calcd for $C_{11}H_9ClN_2O_3$: C, 52.29; H, 3.59; N, 11.00. Found: C, 52.09; H, 3.55; N, 10.78.

Ethyl 3-Phenyloxindole-3-carboxylate (3a).—A solution of 31 g (0.1 mol) of ethyl 3-nitro-3-phenyl-3*H*-indole-2-carboxylate (23a) in 500 ml of methylene chloride and 250 ml of ethanol was treated with 100 ml of ethanol containing 5% of hydrogen chloride. After sitting at room temperature for 20 hr the solvents were evaporated and the residue was crystallized from ether to yield 17 g (60%) of product: mp 156–158°; uv λ_{max} 254 mμ (ε 7800), infl 265 (5600), 289 (1800); ir (KBr) 1740, 1720, 1684 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.17 (t, 3, J = 7 Hz, CH_3), 4.21 (q, 2, J = 7 Hz, CH_2), 7.3 (s, 5, C_6H_5), 6.8–7.6 (m, 4, aromatic H).

Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.56; H, 5.44; N, 4.99.

Similarly the following were prepared.

Ethyl 5-chloro-3-phenyloxindole-2-carboxylate (3c) was obtained in 55% yield by crystallization and chromatography of the mother liquor on silica gel using 10% ethyl acetate in methylene chloride: mp 186–188°, crystallized from ethyl acetate–hexane; uv λ_{max} 259 mμ (ε 11,800), 300 (1800); ir (KBr) 1740, 1720, and 1680 cm^{-1} (CO).

Anal. Calcd for $C_{17}H_{14}ClNO_3$: C, 64.67; H, 4.50; N, 4.44. Found: C, 64.50; H, 4.41; N, 4.27.

Ethyl 5,7-dichloro-3-phenyloxindole-2-carboxylate (3g) (72.5% yield) had mp 182–183°, crystallized from methylene chloride–hexane; uv λ_{max} 258 mμ (ε 11,600), 303 (2200).

Anal. Calcd for $C_{17}H_{13}Cl_2NO_3$: C, 58.31; H, 3.74; N, 4.00. Found: C, 58.31; H, 3.78; N, 4.02.

Ethyl 6,7-dichloro-3-phenyloxindole-3-carboxylate (3i) (89% yield) had mp 238–239°, crystallized from ethanol–ethyl acetate; uv λ_{max} 257 mμ (ε 6300), infl 269 (4500), 294 (2100), sh 300 (2000).

Anal. Calcd for $C_{17}H_{13}Cl_2NO_3$: C, 58.31; H, 3.74; N, 4.00. Found: C, 58.07; H, 3.52; N, 4.02.

Ethyl 4,7-dichloro-3-phenyloxindole-3-carboxylate (3h) (43% yield) had mp 200–203°, crystallized from ethyl acetate; uv λ_{max} 248 mμ (ε 8250), 255 (8350), infl 268 (5000), 295 (1975), 301 (1950).

Anal. Calcd for $C_{17}H_{13}Cl_2NO_3$: C, 58.31; H, 3.74; N, 4.00. Found: C, 58.43; H, 3.61; N, 3.97.

Ethyl 5,7-dimethyl-3-phenyloxindole-3-carboxylate (3k) (55% yield) had mp 199–201°, crystallized from ethyl acetate–hexane; uv λ_{max} 259 mμ (ε 7300), 298 (2040).

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.83; H, 6.19; N, 4.53. Found: C, 78.83; H, 6.25; N, 4.80.

Ethyl 5-Chloro-3-(2-fluorophenyl)oxindole-3-carboxylate (3d).—A 7.05-g (0.02 mol) portion of ethyl 3,5-dichloro-3-(2-fluorophenyl)-3*H*-indole-2-carboxylate (2d) was dissolved in 100 ml of ethanol by gentle warming. After the exothermic reaction, the solvent was evaporated and the residue was crystallized from ether to yield 6.4 g (95%) of product: mp 177–179°; uv λ_{max} 257 mμ (ε 10,980), 299 (1700).

Anal. Calcd for $C_{17}H_{13}ClFNO_3$: C, 61.18; H, 3.92; N, 4.20. Found: C, 60.99; H, 3.60; N, 4.09.

Ethyl 5-Chloro-3-methyloxindole-3-carboxylate (3f).—A 9-ml portion of *tert*-butyl hypochlorite was added to a solution of 12 g (0.05 mol) of ethyl 5-chloro-3-methylindole-2-carboxylate (1f). After sitting for 10 min the solvent was evaporated below 30°. Crystallization from ether–hexane yielded unstable ethyl 3,5-dichloro-3-methyl-3*H*-indole-2-carboxylate (2f): nmr ($CDCl_3$) δ 1.43 (t, 3, J = 7 Hz, CH_3), 2.0 (s, 3, CH_3), 4.46 (q, 2, J = 7 Hz, CH_2), 7.2–7.8 (m, 3, aromatic H).

The collected crystals were dissolved and refluxed for 10 min in 100 ml of ethanol. Chromatography of the residue obtained after evaporation on 200 g of silica gel using 10% ethyl acetate in methylene chloride yielded 5.5 g (43%) of product: mp 120–122°; uv λ_{max} 254 mμ (ε 12,980), 294 (1550); nmr ($CDCl_3$) δ 1.2 (t, 3, J = 7 Hz, CH_3), 1.7 (s, 3, CH_3), 4.2 (q, 2, J = 7 Hz, CH_2), 6.8–7.45 (m, 3, aromatic H), 9.65 (broad s, 1, NH).

Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; N, 5.52. Found: C, 51.09; H, 4.70; N, 5.54.

Without characterization of the 3-chloroindolenines the following were similarly prepared.

***N,N*-Diethyl-5-chloro-3-phenyloxindole-3-carboxamide** (8c) was obtained in 80% yield by first treating 2.4 g (7.3 mmol) of *N,N*-diethyl-5-chloro-3-phenylindole-2-carboxylate (6c) in 50 ml of CH_2Cl_2 with 1.2 ml (10.5 mmol) of *tert*-butyl hypochlorite for 30 min at room temperature and then refluxing the residue obtained upon evaporation in 50 ml of ethanol for 1 hr. Evaporation of the ethanol and crystallization from acetone–hexane gave 2 g of product: mp 130–133°; uv λ_{max} 262 mμ (ε 9100), 300 (1700); nmr ($CDCl_3$) δ 1 (broad s, 6, 2 CH_3), 3.34 (broad s, 4, 2 CH_2), 6.74 (d, 1, J = 8 Hz, C_7 H), 7–7.6 (m, 7, C_6H_5 and C_4 H, C_6 H), 11.0 (broad s, 1, NH).

Anal. Calcd for $C_{19}H_{19}ClN_2O_2$: C, 66.57; H, 5.59; N, 8.17. Found: C, 66.59; H, 5.70; N, 8.19.

1-(6,7-Dichloro-3-phenyloxindole-3-carbonyl)morpholine (8i).—A solution of 3.75 g (0.01 mol) of 1-(6,7-dichloro-3-phenylindole-2-carbonyl)morpholine (6i) in 50 ml of methylene chloride was treated with 1.6 ml (0.014 mol) of *tert*-butyl hypochlorite for 30 min at room temperature. The residue obtained after evaporation was refluxed in 50 ml of ethanol for 1 hr. Removal of the solvent and crystallization of the residue from methylene chloride–ethyl acetate yielded 3.1 g (79%) of product: mp 241–243°; uv λ_{max} 216 mμ (ε 32,600), sh 260 (4600), 292 (1780).

Anal. Calcd for $C_{19}H_{16}Cl_2N_2O_3$: C, 58.33; H, 4.12; N, 7.16. Found: C, 58.61; H, 4.43; N, 7.12.

1-(3-Methyloxindole-3-carbonyl)pyrrolidine (8b) was obtained in 75% yield by first treating 4.6 g (0.02 mol) of 1-(3-methylindole-2-carbonyl)pyrrolidine (6b) in 60 ml of methylene chloride with 3 ml (0.026 mol) of *tert*-butyl hypochlorite for 30 min and then refluxing the crude 3-chloroindolenine in 50 ml of ethanol for 15 min. Evaporation and crystallization from ether yielded 3.7 g of product: mp 218–220°; uv λ_{max} 251 mμ (ε 8190), 282 (1560).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.01; H, 6.73; N, 11.62.

N-Ethyl-5-chloro-3-(2-fluorophenyl)oxindole-3-carboxamide (8e).—A mixture of 3.5 g (0.01 mol) of *N*-ethyl-3,5-dichloro-3-(2-fluorophenyl)-3*H*-indole-2-carboxamide (7e), 100 ml of ethanol, and 3 ml of 1.5 *N* ethanolic hydrogen chloride was heated to boiling. Evaporation and crystallization from ethyl acetate–methanol yielded 2.45 g (74%) of product: mp 228–230°; uv λ_{max} 260 mμ (ε 10,150), infl 269 (7850), 295 (1780); nmr (DMSO-d_6) δ 1.0 (t, 3, J = 7 Hz, CH_3), 3.16 (m, 2, $NHCH_2$–), 6.7–7.5 (m, 7, aromatic H), 7.7 (t, 1, J = 6 Hz, $NHCH_2$, exchanged slowly with D_2O), 11.0 (broad s, 1, NHCO).

Anal. Calcd for $C_{17}H_{14}ClFN_2O_2$: C, 61.36; H, 4.24; N, 8.42. Found: C, 61.41; H, 4.26; N, 8.42.

5-Chloro-3-(2-fluorophenyl)oxindole-3-carboxamide (8d) was obtained in 53% yield by refluxing 3.2 g of 3,5-dichloro-3-(2-fluorophenyl)-3*H*-indole-2-carboxamide (7d) with 100 ml of ethanol containing 3 ml of 1.5 *N* ethanolic hydrogen chloride for 10 min: mp 250–253°, crystallized from tetrahydrofuran–methanol; uv λ_{max} 260 mμ (ε 11,000), infl 270 (8300), 295 (1900); nmr (DMSO-d_6) δ 6.8–7.5 (m, 7, aromatic H), 7.76 (broad s, 2, NH_2, slowly exchanged with D_2O), 11.0 (s, 1, NHCO).

Anal. Calcd for $C_{15}H_{10}ClFN_2O_2$: C, 59.13; H, 3.31; N, 9.19. Found: C, 59.07; H, 3.75; N, 9.08.

5-Chloro-3-phenyloxindole[18] (12). A.—A mixture of 2 g of 2-acetyl-3,5-dichloro-3-phenyl-3*H*-indole (10) and 30 ml of methanol was refluxed for 10 min. Evaporation and crystallization from ether yielded 1.3 g (81%) of product, melting point and spectroscopic data in agreement with those reported in the literature.[18]

B.—A mixture of 0.5 g of ethyl 5-chloro-3-phenyloxindole-3-carboxylate (3c), 10 ml of ethanol, and 1 ml of 50% aqueous potassium hydroxide was heated to reflux for 20 min. The ethanol was evaporated and the residue was partitioned between methylene chloride and dilute hydrochloric acid. The organic layer was dried and evaporated. Crystallization from methylene chloride–ether yielded 0.2 g of 5-chloro-3-phenyloxindole.

5-Chloro-2-ethoxy-3-phenylindole (11). A.—A mixture of 2 g of 2-acetyl-3,5-dichloro-3-phenyl-3*H*-indole (10), 30 ml of methylene chloride, and 10 ml of ethanol was allowed to sit at room temperature for 15 min. The reaction mixture was washed with 10% aqueous sodium carbonate, dried, and evaporated. Crystallization from ethanol–water yielded 1.6 g (90%) of product, mp 124–127°. The analytical sample was recrystallized twice from EtOH–H_2O, mp 127–129°.

Anal. Calcd for $C_{16}H_{14}ClNO$: C, 70.72; H, 5.19; N, 5.16. Found: C, 71.04; H, 5.34; N, 5.09.

Uv λ_{max} 228 mμ (ε 30,700), 281 (17,900); nmr ($CDCl_3$) δ 1.27 (t, 3, J = 7 Hz, CH_3), 4.03 (q, 2, J = 7 Hz, OCH_2), 6.9–8.0 (m, 9, aromatic H and NH).

B.—A suspension of 1.35 g of 5-chloro-3-phenylindole-2-carboxylic acid[17] in 20 ml of methylene chloride was treated with 1 ml of *tert*-butyl hypochlorite. After 5 min, 10 ml of ethanol was added while the temperature was kept at 15–20° by cooling with ice water. After 15 min, the reaction mixture was washed with 10% aqueous sodium carbonate solution. The methylene chloride layer was dried and evaporated. Chromatography of the residue over 30 g of silica gel with benzene and crystallization from hexane yielded 0.5 g (37%) of product, mp 127–129°.

6,7-Dichloro-2-methoxy-3-phenylindole (15).—A 1-ml portion of *tert*-butyl hypochlorite was added to a suspension of 1.5 g of 6,7-dichloro-3-phenylindole-2-carboxylic acid (5i) in 30 ml of methylene chloride. After stirring for 5 min, 20 ml of methanol was added and stirring was continued for 10 min. Work-up as described above yielded after chromatography over 30 g of silica gel using benzene 0.4 g (27%) of product, mp 115–118°.

Anal. Calcd for $C_{15}H_{11}Cl_2NO$: C, 61.67; H, 3.80; N, 4.79. Found: C, 61.49; H, 3.62; N, 4.71.

Uv λ_{max} 234 mμ (ε 23,000), 277–278 (14,400); nmr ($CDCl_3$) δ 3.86 (s, 3, OCH_3), 7–7.8 (m, 7, aromatic H), 8.05 (broad s, 1, NH).

Reaction of 3-Acetyl-3,5-dichloro-3-phenyl-3*H*-indole (10) with Trifluoroacetic Acid.—A 2-ml portion of trifluoroacetic acid was added to a solution of 2 g of 2-acetyl-3,5-dichloro-3-phenyl-3*H*-indole (10) in 20 ml of methylene chloride. After standing at room temperature for 1 hr, the reaction mixture was evaporated, at the end azeotropically with benzene. The residue was chromatographed over 40 g of silica gel using methylene chloride–hexane (1:1). Crystallization of the less polar main component from hexane–ether yielded 0.86 g (50%) of 2,5-dichloro-3-phenylindole (13), mp 89–91°.

Anal. Calcd for $C_{14}H_9Cl_2N$: C, 64.15; H, 3.46; N, 5.34. Found: C, 64.35; H, 3.59; N, 5.28.

Uv λ_{max} 230 mμ (ε 31,800), 270 (11,600), infl 283 (10,750), infl 290 (9400), 301 (7250); ir ($CHCl_3$) 3460 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.0–7.95 (m, 8, aromatic H).

Crystallization of the more polar component from ether yielded 0.18 g (9%) of 1-acetyl-2,5-dichloro-3-phenylindole (14), mp 153–154°.

Anal. Calcd for $C_{16}H_{11}Cl_2NO$: C, 63.18; H, 3.65; N, 4.61. Found: C, 62.87; H, 3.63; N, 4.63.

Uv λ_{max} 243 mμ (ε 23,100), 280 (11,500), 299 (8600), 309 (8050); ir ($CHCl_3$) 1700 cm^{-1} (CO); nmr ($CDCl_3$) δ 2.85 (s, 3, $COCH_3$), 7.1–7.7 (m, 7, aromatic H), 8.33 (d, 1, J = 9 Hz, C_7 H).

A 0.1-g portion of 1-acetyl-2,5-dichloro-3-phenylindole (14) was refluxed for 5 min in 5 ml of ethanol containing 1 ml of 1 *N* aqueous sodium hydroxide. Evaporation, extraction with ether, and crystallization from ether–hexane yielded 0.55 g of 2,5-dichloro-3-phenylindole (13).

A mixture of 0.3 g of 2,5-dichloro-3-phenylindole (13), 2 ml of pyridine, and 0.5 ml of acetic anhydride was heated to reflux for 10 min. The crystals separated from the cooled reaction mixture were collected and recrystallized from ethanol, melting point and mixture melting point identical with those of 1-acetyl-2,5-dichloro-3-phenylindole (14).

A mixture of 0.8 g of 5-chloro-3-phenyloxindole (12) and 10 ml of phosphorus oxychloride was refluxed for 4 hr. The reagent was removed under reduced pressure and the residue was partitioned between benzene and 1 *N* sodium hydroxide solution. The benzene layer was dried and evaporated. Chromatography of the residue on 10 g of silica gel with hexane–methylene chloride (1:1) yielded 0.179 g of 2,5-dichloro-3-phenylindole (13), melting point and mixture melting point identical with those of material obtained before.

2-Nitro-3-phenylindole (24a).—A 5-ml portion of trifluoroacetic acid was added to a solution of 10 g of 2-acetyl-3-nitro-3-phenyl-3*H*-indole (23a) in 100 ml of methylene chloride. After sitting for 1 hr at room temperature the mixture was evaporated under reduced pressure and the residue was crystallized from hexane to yield 6.8 g (80%) of yellow crystals. The analytical sample was recrystallized from acetone–hexane, mp 160–162°.

Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.75. Found: C, 70.67; H, 4.29; N, 11.72.

Uv λ_{max} 237–238 mμ (ε 14,900), 351–352 (13,250); ir (KBr) 3250 (NH), 1555 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 7–8 (m, 9, aromatic H), 9.24 (broad s, 1, NH).

5-Chloro-2-nitro-3-phenylindole (24c).—A mixture of 2 g of 2-acetyl-5-chloro-3-nitro-3-phenyl-3*H*-indole (23c), 20 ml of methylene chloride, and 2 ml of trifluoroacetic acid was allowed to sit at room temperature for 1 hr. Crystals started to separate after 10 min. The suspension was diluted with hexane and the crystals were collected to yield 1.2 g (69%) of product, mp 201–203°.

Anal. Calcd for $C_{14}H_9ClN_2O_2$: C, 61.67; H, 3.33; N, 10.27. Found: C, 61.54; H, 3.21; N, 10.17.

Uv λ_{max} 234–235 mμ (ε 18,150), infl 253 (12,800), 349–350 (1400); ir ($CHCl_3$) 3450 (NH), 1520 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 7.2–7.8 (m, 8, aromatic H), 9.4 (broad s, 1, NH).

5-Chloro-3-methyl-2-nitroindole (24f).—A solution of 5 g of 2-acetyl-5-chloro-3-methyl-3-nitro-3*H*-indole (23f) in 20 ml of trifluoroacetic acid was allowed to sit at room temperature for 15 min. The separated crystals were collected and washed with acetic acid and methanol to leave 3.9 g (93%) of yellow crystals, mp 220–222°. The analytical sample was recrystallized from acetone–methylene chloride, mp 224–226°.

Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.35; N, 13.29. Found: C, 51.25; H, 3.42; N, 13.19.

Uv λ_{max} 246 mμ (ε 8700), 346 (16,560); ir (KBr) 3400 (NH), 1560 cm^{-1} (NO_2); nmr (DMSO-d_6) δ 2.53 (s, 3, CH_3), 7.32 (s with fine structure, 2, C_6 H and C_7 H), 7.65 (s with fine structure, 1, C_4 H), 12.4 (broad s, 1, NH).

Reaction of *trans*-Ethyl 3-(3,5-Dichloro-3-methyl-3*H*-2-indolyl)propenoate (18) with Ethanol.—A mixture of 2 g of *trans*-ethyl 3-(3,5-dichloro-3-methyl-3*H*-2-indolyl)propenoate (18), 20 ml of methylene chloride, and 10 ml of ethanol was allowed to sit at room temperature for 2 hr. The solvents were removed under reduced pressure and the residue was chromatographed over 60 g of silica gel using methylene chloride–hexane (2:1,

(18) H. Kuch, G. Seidl, and K. Schmitt, *Arch. Pharm. (Weinheim)*, **300**, 299 (1967).

v/v). Crystallization of the first eluted compound from ethanol yielded 0.2 g (10%) of ethyl 2-chloro-3-(5-chloro-3-methyl-2-indolyl)propenoate (**20**) as yellow crystals, mp 155–157°.

Anal. Calcd for $C_{14}H_{13}Cl_2NO_2$: C, 56.40; H, 4.40; N, 4.70. Found: C, 56.26; H, 4.28; N, 4.65.

Uv λ_{max} 262 mμ (ε 9670), 355–357 (ε 33,200); ir (KBr) 3440 (NH), 1710 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.4 (t, 3, J = 7 Hz, CH_3), 2.4 (s, 3, CH_3), 4.45 (q, 2, J = 7 Hz, CH_2), 7.28 (s with fine structure, 2, C_6 H and C_7 H), 7.55 (s with fine structure, 1, C_4 H), 7.99 (s, 1, β proton).

Crystallization of the later eluted second component from hexane yielded 0.9 g (39%) of ethyl 2-chloro-3-(5-chloro-3-methyl-2-indolyl)-3-ethoxypropanoate (**19**), mp 81–83°.

Anal. Calcd for $C_{16}H_{19}Cl_2NO_3$: C, 55.83; H, 5.56; N, 4.07. Found: C, 55.60; H, 5.48; N, 4.19.

Uv λ_{max} 230 mμ (ε 38,000), 286–287 (8100), 294 (8100), infl 304 (5850); ir ($CHCl_3$) 3470 (NH), 1750 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.13 (t, 3, J = 7 Hz, CH_3), 1.3 (t, 3, J = 7 Hz, CH_2), 2.34 (s, 3, CH_3), 3.52 (q, 2, J = 7 Hz, OCH_2), 4.33 (q, 2, J = 7 Hz, $COOCH_2$–), 4.5 (d, 1, J = 9 Hz), and 5.05 (d, 1, J = 9 Hz) (AB system, α and β proton), 7–7.5 (m, 2, C_6 H and C_7 H), 7.53 (s with fine structure, 1, C_4 H), 8.33 (broad s, 1, NH).

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Registry No.—**1g**, 40735-51-1; **1h**, 40735-52-2; **1i**, 40735-53-3; **1k**, 40735-54-4; **2c**, 40735-55-5; **2d**, 40735-56-6; **2f**, 40735-57-7; **3a**, 40735-58-8; **3c**, 40735-59-9; **3d**, 40735-60-2; **3f**, 40735-61-3; **3g**, 40735-62-4; **3h**, 40735-63-5; **3i**, 40735-64-6; **3k**, 40827-74-5; **5d**, 40731-34-8; **5f**, 16381-47-8; **5i**, 40731-36-0; **6b**, 40731-37-1; **6c**, 40731-38-2; **6d**, 24106-90-9; **6e**, 40730-98-1; **6f**, 40730-99-2; **6i**, 40731-00-8; **7d**, 40731-01-9; **7e**, 40731-02-0; **8b**, 40731-03-1; **8c**, 40731-04-2; **8d**, 40731-05-3; **8e**, 40731-06-4; **8i**, 40731-07-5; **9c**, 40731-08-6; **9f**, 40731-09-7; **10**, 40731-10-0; **11**, 40731-11-1; **12**, 15815-97-1; **13**, 40731-13-3; **14**, 40731-14-4; **15**, 40731-15-5; **16**, 40731-16-6; **17**, 40731-17-7; **18**, 40827-72-3; **19**, 40731-18-8; **20**, 40731-19-9; **21a**, 40731-20-2; **21c**, 40731-21-3; **21g**, 40827-73-4; **21h**, 40731-22-4; **21i**, 40731-23-5; **21k**, 40731-24-6; **23a**, 40731-25-7; **23c**, 40731-26-8; **23f**, 40731-27-9; **24a**, 40731-28-0; **24c**, 40731-29-1; **24f**, 40731-30-4; phosphorus pentachloride, 10026-13-8; methylene chloride, 75-09-2; thionyl chloride, 7719-09-7; *tert*-butyl hypochlorite, 507-40-4; ethyl 5-chloro-3-phenylindole-2-carboxylate, 21139-32-2; ethyl 3-phenylindole-2-carboxylate, 37129-23-0; 2-acetyl-3-phenylindole, 36015-23-3; trifluoroacetic acid, 76-05-1; ethanol, 64-17-5.

Supplementary Material Available.—Listings of structure factors coordinates, and thermal parameters for **21c** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3077.

Synthesis of 1,2-Diaminobenzimidazole, 1*H*-*s*-Triazolo[1,5-*a*]benzimidazoles, and *as*-Triazino[2,3-*a*]benzimidazoles

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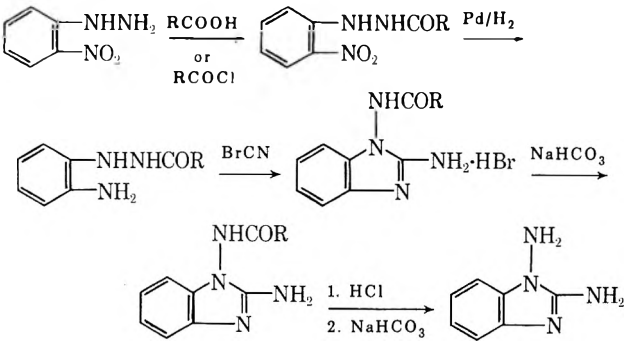
The preparations of 1,2-diaminobenzimidazole, a new compound, and of two new ring systems, 1*H*-*s*-triazolo[1,5-*a*]benzimidazole and *as*-triazino[2,3-*a*]benzimidazole, are reported.

Although 1-aminobenzimidazoles are relatively well-known compounds[1] and 2-aminobenzimidazoles have been known for a longer period of time,[2] nothing has been reported on 1,2-diaminobenzimidazole and its derivatives. The 1,2-diaminobenzimidazoles are readily obtained from *o*-acylhydrazidoanilines and cyanogen bromide.



The *o*-nitrophenylhydrazines were obtained from the corresponding *o*-nitroanilines by diazotization followed by reduction with sodium bisulfite.[3] The catalytic hydrogenation proceeded smoothly as long as the *o*-acylhydrazidonitrobenzene was pure. The ring-closure step was carried out by adding the cyanogen bromide to a suspension of the *o*-acylhydrazidoaniline in water. All of the ring compounds, isolated from the cyanogen bromide reactions, had the uv absorptions characteristic of benzimidazoles, namely 240–250 mμ for the amidine group and 280–300 mμ for the benzenoid portion.[4]

Heating the 1-acylamido-2-aminobenzimidazoles with acid anhydrides or acid chlorides produced 1*H*-*s*-triazolo[1,5-*a*]benzimidazoles (a new ring system). The R groups at positions 1 and 2 were always found to be identical with the R group of the acid anhydride or chloride.[1b] It would appear from this observation that ring closure is slow compared to the rate of trans acylation. It is interesting to note that the action of hydrochloric acid on the 1-acylamido-2-aminobenzimidazoles did not bring about the formation of the triazolo compound (Phillips method).[5]

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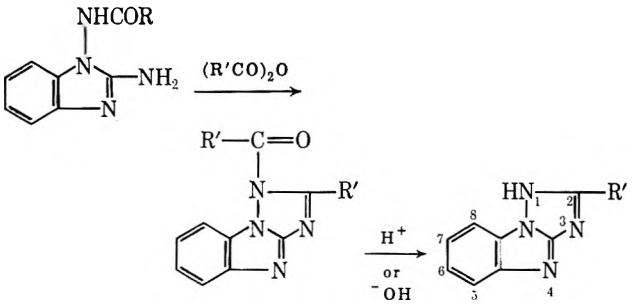
(2) N. J. Leondard, D. Y. Curtin, and K. M. Beck, *J. Amer. Chem. Soc.*, **69**, 2459 (1947).

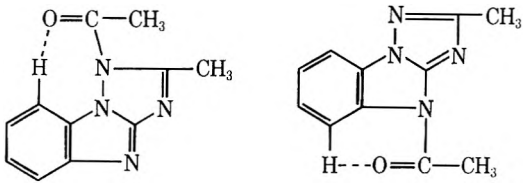
(3) W. Davis, *J. Chem. Soc.*, **121**, 720 (1922); C. Montigel and T. Reichstein, *Helv. Chim. Acta*, **20**, 1468 (1937).

(4) K. Hofmann, Ed., "Imidazole and Derivatives," part 1, Interscience, New York, N. Y., 1953, p 253; A. Mangini and F. Montanari, *Bull. Sci. Fac. Chim. Ind. Bologna*, **14**, 36 (1956).

(5) M. A. Phillips, *J. Chem. Soc.*, 3134 (1928); 2820 (1929); 1409 (1930).

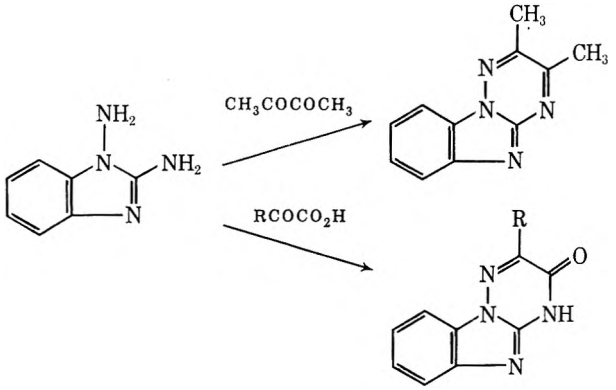


Owing to the tautomeric nature of 1*H*-*s*-triazolo-[1,5-*a*]benzimidazole, there are three theoretically possible isomeric structures for the monoacyl derivatives. The assignment of the acyl group to the 1 position is therefore somewhat arbitrary. Only a single isomer was obtained by ring closure and the same isomer was obtained by acylation of 1*H*-*s*-triazolo[1,5-*a*]benzimidazole. The nmr spectrum ($CHCl_3$) for the acetyl derivative shows a singlet at δ 2.46 (3 H, CH_3CO), a singlet at 2.83 (3 H, CH_3), a multiplet centered at 7.4 (3 H, aromatic), and a multiplet centered at 8.5 (1 H, in 8 or 5 position). The unusual shift of one proton is probably due to a long-range anisotropic effect. This shift was noted only for the acyl derivatives and was not observed for 1*H*-*s*-triazolo[1,5-*s*]benzimidazole or its 2-alkyl derivatives. The nmr data appear to fit either the 1-acetyl or 4-



acetyl derivative. Benzylation of 1*H*-*s*-triazolo-[1,5-*a*]benzimidazole also gave only one isomer.

1,2-Diaminobenzimidazole reacted with 2,3-butanedione to form 2,3-dimethyl-*as*-triazino[2,3-*a*]-benzimidazole. Reactions with pyruvic acid and benzoylformic acid gave 2-methyl-*as*-triazino[2,3-*a*]benzimidazol-3(4*H*)-one and 2-phenyl-*as*-triazino[2,3-*a*]-benzimidazol-3(4*H*)-one, respectively. The dialkyl derivatives were yellow solids while the derivatives of the α-keto acids were colorless solids which show an intense amide carbonyl at 1700 cm^{-1}.



Experimental Section

Melting points, up to 270°, were taken on a Thomas-Hoover capillary melting point apparatus. Above 270°, they were taken on a copper block melting point apparatus. The melting points are uncorrected. Ir spectra were obtained with a Perkin-Elmer Model 521 spectrophotometer and uv spectra were measured with a Cary 14 spectrophotometer. Nmr spectra were determined at 60 Mcps on a Varian Associates NMR Model HA-60.

1-Formamido-2-aminobenzimidazole Hydrobromide (1).—A solution of 1.5 g (0.0142 mol) of cyanogen bromide in a little water was added to a suspension of 2.12 g (0.0142 mol) of *o*-formylhydrazidoaniline[1b] in 30 ml of water. The mixture was stirred for 2 hr at 0° and then for 5 hr at room temperature. The solvent was removed under reduced pressure. The residual dark oil was triturated alternately with dry ethanol and dry benzene until it solidified, yield 85%. We were unable to purify this compound because of its hygroscopic nature. That it was at least 95% pure 1-formamido-2-aminobenzimidazole hydrobromide was shown by the fact that a 95% yield of monopicrate was obtained in methanol solution. This is the yield after recrystallization from water–dimethylformamide: mp 270–275°.

Anal. Calcd for $C_{14}H_{11}N_7O_8$: C, 41.50; H, 2.70; N, 24.10. Found: C, 41.31; H, 2.54; N, 24.23.

1-Acetamido-2-aminobenzimidazole Hydrobromide (2).—The acetamido derivative was prepared from o-acethydrazidoaniline[1b] by the procedure used for compound 1. The residue from the evaporation of the solvent was washed with dry ether and dry acetone and recrystallized from acetonitrile: yield 90% mp 244–246°.

Anal. Calcd for $C_9H_{11}BrN_4O$: C, 39.86; H, 4.09; N, 20.66; Br, 29.47. Found: C, 39.61; H, 4.03; N, 20.43; Br, 29.27.

1-Acetamido-2-aminobenzimidazole Hydrate (3).—An aqueous solution of 2 was neutralized with sodium bicarbonate to precipitate the free base which was recrystallized from water. It was isolated as a monohydrate: yield 82%; mp 224–226°; ir (KBr) strong band at 1700 cm^{-1} (amide carbonyl); nmr (DMSO) singlet at δ 2.06 (3 H, CH_3), singlet at 6.45 (2 H, NH_2), multiplet centered at 7.0 (4 H, aromatic), singlet at 10.5 (1 H, HNC=O). The amide proton, being adjacent to two electron-withdrawing groups, absorbs more downfield than the phenyl protons. The 2-amino and 1-amido proton absorptions disappeared in the presence of D_2O.

Anal. Calcd for $C_9H_{12}N_4O_2$: C, 51.92; H, 5.77; N, 26.92. Found: C, 51.96; H, 5.97; N, 26.96.

The monopicrate, prepared in methanol solution, was recrystallized from acetonitrile: mp 276–283°.

Anal. Calcd for $C_{15}H_{12}N_7O_8$: C, 42.96; H, 3.10; N, 23.39. Found: C, 43.06; H, 3.24; N, 23.23.

1-Propionamido-2-aminobenzimidazole Hydrobromide (4).—Compound 4 was prepared from *o*-propionhydrazidoaniline[1b] by the procedure used for preparing compound 2: yield 66%, mp 221–223°.

Anal. Calcd for $C_{10}H_{13}BrN_4O$: C, 42.28; H, 4.55; N, 19.66; Br, 28.04. Found: C, 42.18; H, 4.69; N, 19.49; Br, 28.02.

1-Propionamido-2-aminobenzimidazole (5).—Free base 5 was prepared from hydrobromide 4 by neutralization with sodium bicarbonate and recrystallization from ethyl acetate: yield 83%, mp 171–173°.

Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.82; H, 5.88; N, 27.42. Found: C, 59.01; H, 5.75; N, 27.25.

1-Benzamido-2-aminobenzimidazole Hydrobromide (6).—Compound 6 was prepared from o-benzoylhydrazidoaniline[1b] by the procedure used for preparing compound 2: yield 80%, mp 245–247°.

Anal. Calcd for $C_{14}H_{13}BrN_4O$: C, 50.43; H, 3.93; N, 16.81; Br, 23.98. Found: C, 50.59; H, 4.01; N, 16.79; Br, 24.06.

The monopicrate, prepared in methanol solution, was recrystallized from acetonitrile: mp 270–280°.

Anal. Calcd for $C_{20}H_{15}N_7O_8$: C, 49.89; H, 3.13; N, 20.37. Found: C, 50.1; H, 3.29; N, 20.23.

1,2-Diaminobenzimidazole (7).—The 1,2-diamino compound may be prepared by hydrolyzing any of the 1-acylamido-2-aminobenzimidazoles or their hydrobromides. The following is an example. 1-Acetamido-2-aminobenzimidazole hydrobromide (0.5 g) was dissolved in 60 ml of 4 *N* hydrochloric acid and the solution was refluxed for 1 hr. On cooling the hydrochloride separated. The salt was dissolved in water and the solution was neutralized with sodium bicarbonate to precipitate the free base. The free base was recrystallized from ethanol: yield 70%; mp 256–259°; ir (KBr) showed no carbonyl absorption, strong N–H stretching absorptions at 3375 and 3500 cm^{-1};

nmr (DMSO) singlet at δ 5.52 (2 H, 1-NH_2), singlet at 6.15 (2 H, 2-NH_2), multiplet centered at 7.1 (4 H, aromatic protons).

Anal. Calcd for $C_7H_8N_4$: 56.75; H, 5.42; N, 37.92. Found: C, 56.80; H, 5.52; N, 37.76.

1-Acetyl-2-methyl-1*H*-*s*-triazolo[1,5-*a*]benzimidazole (8).—1-Acetamido-2-aminobenzimidazole hydrobromide (0.5 b, 0.0018 mol) was dissolved in 60 ml of acetic anhydride and the solution was refluxed for 5 hr. The solution was reduced to 5–10 ml under reduced pressure. An oil separated which solidified on cooling. The solid was recrystallized from acetonitrile: yield 71%; mp 154–155°; ir (KBr) strong band at 1700 cm^{-1} for amide carbonyl.

Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.70; H, 4.67; N, 26.17. Found: C, 61.67; H, 4.58; N, 25.98.

2-Methyl-1*H*-*s*-triazolo[1,5-*a*]benzimidazole (9).—1-Acetyl-2-methyl-1*H*-*s*-triazolo[1,5-*a*]benzimidazole (0.5 g) was dissolved in 80 ml of hydrochloric acid and the solution was refluxed for 2 hr. The solution was evaporated to 10–15 ml and neutralized with sodium bicarbonate. The precipitate was removed, washed with water, and recrystallized from acetonitrile: yield 80%; mp 258–259°; nmr (CD_3COOD) singlet at δ 2.5 (3 H, CH_3), multiplet centered at 7.5 (4 H, aromatic).

Anal. Calcd for $C_9H_8N_4$: C, 62.78; H, 4.65; N, 32.56. Found: C, 62.64; H, 4.53; N, 32.47.

1-Propionyl-2-ethyl-1*H*-*s*-triazolo[1,5-*a*]benzimidazole (10).—1-Propionamido-2-aminobenzimidazole hydrobromide was refluxed with propionic anhydride. The procedure for **8** was followed to obtain **10**: yield 71%; mp 111–113°; ir (KBr) 1700 cm^{-1} (amide carbonyl); nmr ($CDCl_3$) triplet at δ 1.37 (3 H, 2-CH_3), quartet at 2.9 (2 H, 2-CH_2), triplet at 1.42 (3 H, 1-CH_3), quartet at 3.4 (2 H, 1-CH_2), multiplet at 7.55 (3 H, aromatic protons 5, 6, 7), singlet at 8.55 (1 H, aromatic proton 8).

Anal. Calcd for $C_{13}H_{14}N_4O$: C, 64.47; H, 5.80; N, 23.14. Found: C, 64.34; H, 5.84; N, 23.00.

2-Ethyl-1*H*-*s*-triazolo[1,5-*a*]benzimidazole (11).—This compound was prepared from **10** by the procedure used for making **9**. The product was recrystallized from ethyl acetate: yield 66%; mp 198–200°: nmr (CD_3COOD) triplet at δ 1.4 (3 H, 2-CH_3), quartet at 2.85 (2 H, 2-CH_2), multiplet at 7.55 (4 H, aromatic protons).

Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.45; H, 5.41; N, 30.00. Found: C, 64.51; H, 5.31; N, 30.19.

1-Benzoyl-2-phenyl-1-*H*-*s*-triazolo[1,5-*a*]benzimidazole (12).—1-Benzamido-2-aminobenzimidazole (0.5 g) was dissolved in 60 ml of benzoyl chloride and the solution was refluxed for 5 hr. The solution was distilled under reduced pressure to 5–10 ml and the resulting oil was cooled until it solidified. The product was washed with dry ether and recrystallized from acetonitrile: yield 83%; mp 230–232°; ir (KBr) 1700 cm^{-1} (amide carbonyl); nmr ($CDCl_3$) multiplet at δ 7.37 (3 H, protons 5, 6, 7), multiplet at 7.54 (5 H, C_6H_5), multiplet at 8.04 (5 H, $C_6H_5C{=}O$), multiplet at 8.43 (1 H, proton 8).

Anal. Calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.54; N, 18.05. Found: C, 77.51; H, 4.65; N, 17.88.

2-Phenyl-1*H*-*s*-triazolo[1,5-*a*]benzimidazole (13).—1-Benzoyl-2-phenyl-1*H*-*s*-triazolo[1,5-*a*]benzimidazole (0.5 g) was dissolved in 40 ml of 10% sodium hydroxide and the solution was refluxed for 2 hr. The solution was evaporated almost to dryness and the residue was extracted with ethyl acetate. Distillation of the ethyl acetate left a colorless solid which was recrystallized from ethanol: yield 60%; mp 310–315°; nmr (CD_3COOD) multiplet at δ 7.54 (4 H, aromatic), multiplet at 8.00 (5 H, aromatic).

Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.78; H, 4.27; N, 23.92. Found: C, 71.84; H, 4.15; N, 23.76.

1-Benzyl-2-phenyl-1*H*-*s*-triazolo[1,5-*a*]benzimidazole (14).—2-Phenyl-1*H*-*s*-triazolo[1,5-*a*]benzimidazole (0.63 g, 0027 mol) was dissolved in dry dimethylformamide. Sodium hydride (0.065 g, 0.0077 mol) was added gradually with stirring. The mixture was gently refluxed for 40 min and 0.38 g (0.003 mol) of benzyl chloride was added. Refluxing was continued for 2 hr and the solution was cooled to 5°. The addition of 10 ml of water precipitated a solid which was recrystallized from *n*-hexane: yield 50%; mp 130–132°; nmr (CCl_4) singlet at δ 5.38 (2 H, CH_2), multiplet at 7.20 (4 H, aromatic), multiplet at 7.30 (5 H, 2-phenyl group), multiplet at 7.82 (5 H, C_6H_5 of benzyl).

Anal. Calcd for $C_{21}H_{16}N_4$: C, 77.75; H, 4.97; N, 17.27. Found: C, 77.65; H, 5.10; N, 17.27.

2,3-Dimethyl-*as*-triazino[2,3-*a*]benzimidazole (15).—1,2-Diaminobenzimidazole (0.5 g, 0.0035 mol) was dissolved in 60 ml of methanol. A solution of 0.43 g (0.005 mol) of 2,3-butanedione in methanol was added and the solution was refluxed for 2 hr. The methanol was removed *in vacuo* and the residue was recrystallized from ethanol: yield 58%; yellow crystals; mp 236–239°; ir showed no carbonyl or NH absorption.

Anal. Calcd for $C_{11}H_{10}N_4$: C, 66.65; H, 5.09; N, 28.27. Found: C, 66.65; H, 5.08; N, 28.25.

2-Methyl-*as*-triazino[2,3-*a*]benzimidazol-3(4*H*)-one (16).—Pyruvic acid was used in place of 2,3-butanedione and ethanol was the solvent. The product was recrystallized from dimethylformamide: yield 72%, colorless crystals, mp 350–355°.

Anal. Calcd for $C_{10}H_8N_4O$: C, 59.99; H, 4.20; N, 27.82. Found: C, 59.80; H, 4.01; N, 27.76.

2-Phenyl-*as*-triazino[2,3-*a*]benzimidazol-3(4*H*)-one (17).—Benzoylformic acid was used in place of 2,3-butanedione and ethanol was the solvent. The product was recrystallized from dimethylformamide–water: yield 68%, colorless crystals, mp 355–358°.

Anal. Calcd for $C_{15}H_{10}N_4O$: C, 68.67; H, 3.84; N, 21.36. Found: C, 68.48; H, 3.84; N, 21.30.

Registry No.—**1**, 40697-60-7; 1 monopicrate, 40697-61-8; **2**, 40697-62-9; **3**, 40697-63-0; **3** monopicrate, 40697-64-1; **4**, 40697-65-2; **5**, 40697-66-3; **6**, 40697-67-4; **6** monopicrate, 40697-68-5; **7**, 29540-87-2; **8**, 40935-54-4; **8** 4-acetyl tautomer, 40697-70-9; **9**, 40697-71-0; **10**, 40697-72-1; **10** 4-propionyl tautomer, 40697-73-2; **11**, 40697-74-3; **12**, 40736-41-2; **12** 4-benzoyl tautomer, 40736-42-3; **13**, 40697-75-4; **14**, 40697-76-5; **15**, 40697-77-6; **16**, 40697-78-7; **17**, 40697-79-8; **18**, 40697-80-1; cyanogen bromide, 506-68-3; *o*-formhydrazidoaniline, 6299-89-4; *o*-acetylhydrazidoaniline, 6299-91-8; *o*-propionylhydrazidoaniline, 40697-83-4; *o*-benzoylhydrazidoaniline, 6299-88-3; acetic anhydride, 108-24-7; propionic anhydride, 123-62-6; benzoyl chloride, 98-88-4; 2,3-butanedione, 431-03-8; 2,3-pentanedione, 600-14-6; pyruvic acid, 127-17-3; benzoylformic acid, 611-73-4.

Bridgehead Nitrogen Heterocycles. VI. The Synthesis and Characterization of Some Ring-Fused 3-Substituted 3*H*-[1,2,4]Thiadiazolopyrimidines, -pyrazines, and -pyridazines[1a]

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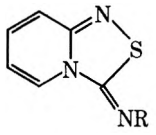
Condensation of the trichloromethylthioamino derivatives of pyridazines, pyrimidines, and pyrazines derived from the corresponding amino compound and perchloromethyl mercaptan with primary aromatic amines gave a variety of 3-substituted derivatives of the new, title ring systems. In several instances transaminations were observed. Spectral characteristics of these derivatives are described.

The 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine ring system **1** was synthesized recently from 2-aminopyridines and perchloromethyl mercaptan.[2a] Isolation of the intermediate trichloromethylthioaminopyridine, followed by reaction with primary, aromatic amines, enabled a wide variety of substituents to be introduced into the 3 position.[2b] Reaction with sodium sulfhydrate and suitable enolate anions greatly extended the scope of this route to this fused-ring system.[2b] The isomeric ring system, 2-substituted 2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyridine (**2**), has also been prepared



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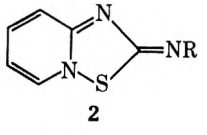

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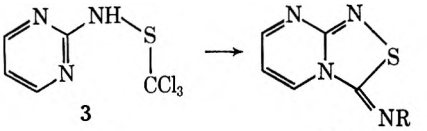
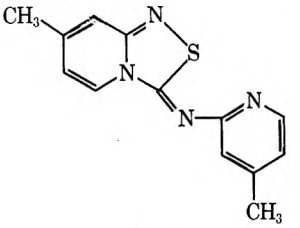
recently[3] by the oxidation of *N*-(2-pyridyl)thioureas with bromine or sulfuryl chloride, and 2-aminobenzothiazole and perchloromethyl mercaptan were found to yield the corresponding [1,2,4]thiadiazolo[3,4-*b*]-benzothiazole system.[4] It was of interest to establish whether the reaction of an appropriate amino heterocycle with perchloromethyl mercaptan is a general route to ring-fused [1,2,4]thiadiazole derivatives, and results obtained in the pyridazine, pyrimidine, and pyrazine systems are described in this communication.

3*H*-[1,2,4]Thiadiazolo[4,3-*a*]pyrimidine (4).—2-Aminopyrimidine has been reported[5] to react with perchloromethyl mercaptan giving 2-trichloromethylthioaminopyrimidine (**3**). Treatment of this sulfenamide with a variety of primary, aromatic amines in chloroform solution gave in moderate yields the 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyrimidine derivatives **4** described in Table I. Reaction of 2-aminopyrimidine and perchloromethyl mercaptan in the ratio of 2:1 gave a small quantity of 3-(2-pyrimidylimino)-3*H*-[1,2,4]-thiadiazolo[4,3-*a*]pyrimidine characterized only by a molecular ion, *m/e* 230, and an infrared absorption at 1620 cm^{-1} (C=N). With 2-amino-4-methylpyridine and **3**, the desired product **4** (R = 4-CH_3-2-C_5H_3N) was obtained together with an equal amount of a product identified as 7-methyl-3-(4-methyl-2-pyridylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine (**5**). This could also be prepared directly from 2-amino-4-methylpyridine and perchloromethyl mercaptan (2:1) as described previously.[2a] This no doubt arose by a transamination reaction in which the more basic 2-amino-4-methylpyridine (pK_a = 7.48)[6] displaced 2-aminopyrimidine (pK_a = 3.45)[7] from **3** forming the corresponding 4-methyl-2-trichloromethylthioaminopyridine (**6**), which then underwent ring closure with 2-amino-4-methylpyridine to **5**. In this study transamination was always observed to some extent when closure was attempted using 2-aminopyridine derivatives, being easily detected by tlc, but only with 2-amino-4-methylpyridine was the quantity of product sufficient for isolation. Related amine exchange in sulfenamides has also been observed[8] with 2-*tert*-butylaminothiobenzothiazole and morpholine on heating in an inert solvent to 100°.

As derivatives of this system decompose near their melting point, difficulties in purification occur with lower melting products. This was especially true in the reactions of **3** with aniline derivatives. For example,



3 **4**



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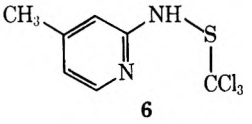

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while those derivatives presented in Table I were easily purified, reaction of **3** with either *p*-toluidine or *p*-chloroaniline yielded products which decomposed upon attempted recrystallization.

The analytical and spectral data described in Tables I and II clearly show that ring closure had occurred to these [1,2,4]thiadiazolo[4,3-*a*]pyrimidines. The possibility that ring closure had occurred in an alternative sense to yield a 2-substituted 2*H*-[1,2,4]thiadiazolo-[2,3-*a*]pyrimidine (**7**) (such would be the case if in **3** the trichloromethylthio group were attached to a ring

(1) (a) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged; (b) NDEA Trainee, 1970–1972.

(2) (a) K. T. Potts and R. Armbruster, *J. Org. Chem.*, **35**, 1965 (1970); (b) *ibid.*, **36**, 1846 (1971).

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(6) F. N. Fastier and M. A. McDowell, *Austr. J. Exptl. Biol.*, **36**, 491 (1968).

(7) A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948).

(8) J. J. D'Amico and D. D. Mullins, *Int. J. Sulfur Chem.*, in press; see also F. A. Davis, R. B. Wetzil, T. J. Devon, and J. F. Starkhouse, *J. Org. Chem.*, **36**, 799 (1971); F. A. Davis, S. Divald, and A. H. Cohn, *Chem. Commun.*, 294 (1971).

TABLE I

SOME RING-FUSED 1,2,4-THIADIAZOLES

Structure	R	Method	Mp, °C[a]	Yield, %	Crystal habit[b]	Solvent[c]	Analysis: Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	M·+ m/e (rel intensity)	Ir, cm⁻¹: C=N-	Ir, cm⁻¹: Thiadiazole ring deformn	Uv: λmax, nm	Uv: Log ε
4	2-Pyridyl	A	226–228	40	N	A	52.38	3.08	30.55	52.30	3.04	30.40	229 (100)	1640	1455	423	3.51
																407	3.53
																337	4.16
																324	4.10
																273	4.02
																252	4.14
4	4-Methyl-2-pyridyl	A	201–202	13	N	B:E	54.30	3.73	28.79	54.22	3.67	28.54	243 (100)	1630	1470	396	3.34
																376	3.29
																329	3.87
																321	3.82
																270	3.75
																247	3.81
4	4,6-Dimethyl-2-pyridyl	A	217–218	10	P	B	56.01	4.31	27.22	55.86	4.15	27.19	257 (100)	1630	1450	415	3.49
																333	4.16
																321[d]	4.15
																308	3.90
																272	4.00
																250	4.11
4	5-Chloro-2-pyridyl	A	249–250	28	Y	A	45.54	2.29	26.56	45.69	2.30	26.55	263 (95)	1640	1475	400	3.68
																341	4.20
																330[d]	4.13
																280	4.12
																247	4.23
4	5-Iodo-2-pyridyl	A	255–256	24	X	C	33.81	1.70	19.72	33.71	1.67	19.65	355 (100)	1630	1460	398	3.77
																343	4.31
																333[d]	4.23
																285	4.15
																245	4.21
4	2,5-Dichlorophenyl	A	199–200	57	N	F	44.46	2.04	18.85	44.42	2.03	18.80	296 (59)	1640	1470	415	3.40
																335[d]	3.52
																292	3.96
																239	4.32
4	3,4-Dichlorophenyl	A	182–184	81	N	F	44.46	2.04	18.85	44.65	2.04	19.16	296 (44)	1630	1470	420	3.46
																332[d]	3.62
																302	4.09
																244	4.24
4	*p*-Nitrophenyl	A	243–244	44	N	G	48.34	2.58	25.63	48.15	2.50	25.47	273 (80)	1630	1470	413	3.99
																360	4.16
																285[d]	3.90
																247	4.33
4	*m*-Nitrophenyl	A	189–191	66	N	G	48.34	2.58	25.63	48.24	2.53	25.53	273 (92)	1630	1470	405	3.49
																300[d]	4.04
																277[d]	4.13
																247	4.33

9	2,6-Dimethyl-4-pyrimidyl	B	182–184	32	Y	B	54.52	4.93	29.35	54.29	4.85	29.18	286 (100)	1640	1440	370	4.17
																328	4.16
																317	4.13
																255[d]	3.96
10	2-Pyrazinyl	B	287–289	30	Y	B	46.94	2.63	36.50	46.78	2.49	36.39	230 (100)	1620	1470	226	4.36
																385[d]	3.82
																358	4.19
																278	4.00
																253[d]	3.99
																242	4.08
12	6-Chloro-3-pyridazinyl	B	240–243	12	Y	B:E	36.13	1.35	28.10	36.22	1.34	28.12	298 (63)	1610	1480	425	3.96
																368	3.94
																253	4.23
12	5-Methyl-2-pyridyl	A	252–254	16	N	S	47.57	2.90	25.22	47.65	3.02	25.16	277 (100)	1610	1470	425	3.39
																338	4.19
																336	4.17
																327	4.26
																315[d]	4.14
																270[d]	4.34
																363	4.36

[a] All decomposed at melting point except 9. [b] N = orange needles; P = orange prisms; Y = yellow, irregular prisms; X = brown, irregular prisms; Z = yellow, matted needles. [c] A = acetone; B = benzene; C = chloroform; D = cyclohexane; E = petroleum ether (bp 60–80); F = ethyl acetate; G = 1,2-dichloroethane; S = sublimed. [d] Shoulder.

TABLE II

NMR DATA FOR SOME REPRESENTATIVE RING-FUSED 1,2,4-THIADIAZOLES

Structure	R	Chemical shift, δ[a]
4	4,6-Dimethyl-2-pyridyl	2.35 (s, 3, 4′-CH_3), 2.60 (s, 3, 6′-CH_3), 6.55 (q, 1, 6-H), 6.70 (m, 1, 5′-H), 7.02 (m, 1, 3′-H), 8.66 (m, 1, 7-H), 8.80 (m, 1, 5-H)
9	2,6-Dimethyl-4-pyrimidyl	2.30 (d, 3, 7-CH_3), 2.48 (s, 3, 6′-CH_3), 2.72 (s, 3, 2′-CH_3), 3.20 (s, 3, 5-CH_3), 6.62 (m, 1, 8-H), 6.88 (m, 1, 5′-H)
10	2-Pyrazinyl	8.02 (m), 8.45 (m), 8.93 (m), 9.02 (m), 9.34 (m), 9.50 (m)
12	5-Methyl-2-pyridyl	2.38 (s, 3, 5′-CH_3), 7.35 (m), 8.40 (m)

[a] All spectra were determined in $CDCl_3$ except 10, where CF_3CO_2D was used.

nitrogen) can be excluded on the basis of the close relationship of the spectral data to that of derivatives of the 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine system.[2]

Steric considerations clearly exert an influence on the ring closure to the fused system, as 2-amino-4,6-dimethylpyrimidine failed to yield a product with perchloromethyl mercaptan in a 2:1 ratio. In contrast to 2-trichloromethylthioaminopyridine, the pyrimidine derivative **3** did not react with sodium sulfhydrate or a variety of enolate anions such as sodium acetylacetonate, most likely owing to ring opening under the alkaline reaction conditions.

3*H*-[1,2,4]Thiadiazolo[4,3-*c*]pyrimidine (**9**).—This ring system could only be prepared from the reaction

7

8

9

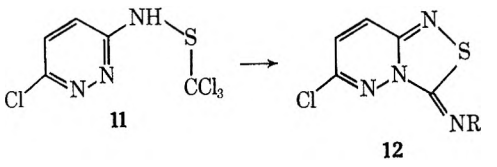
of 4-amino-2,6-dimethylpyrimidine[9] with perchloromethyl mercaptan (2:1) in the presence of triethylamine. All attempts to isolate the postulated 2,6-dimethyl-4-trichloromethylthioaminopyrimidine (**8**) intermediate were unsuccessful. The nmr spectrum of **9** showed four clearly separated methyl resonances at δ 2.30, 2.48, 2.72, and 3.20 and the assignments made in Table II are based on decoupling experiments and on the downfield shift expected for protons or methyl groups adjacent to nitrogen.

3*H*-[1,2,4]Thiadiazolo[4,3-*a*]pyrazine (**10**).—As with the 4-aminopyrimidine derivative above, 2-aminopyrazine could only be converted into 3-(2-pyrazinylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyrazine (**10**) by reaction with perchloromethyl mercaptan in the presence of triethylamine. The intermediate 2-trichloromethylthioaminopyrazine also proved too unstable for isolation and **10** could only be purified by numerous preparative layer chromatograms.

3*H*-[1,2,4]Thiadiazolo[4,3-*b*]pyridazine (**12**).—2-Amino-6-chloropyridazine reacted with perchloromethyl mercaptan to give 6-chloro-2-trichloromethylthioaminopyridazine (**11**), sufficiently pure for further reaction. With 2-amino-5-methylpyridine, ring closure

(9) A. R. Ronzio and W. B. Cook, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 71.

occurred to 6-chloro-3-(5-methyl-2-pyridylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*b*]pyridazine (**12**, R = 5-CH_3-2-C_5H_3N). However, using a 2:1 ratio of the aminopyridazine and perchloromethyl mercaptan gave 6-chloro-3-(6-chloro-3-pyridazinylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*b*]pyridazine (**12**, R = 6-Cl-3-$C_4H_2N_2$). Preparative layer chromatography was necessary to effect satisfactory purification of both derivatives.



Spectral Characteristics.—Infrared bands common to all compounds were observed at 1610–1640 and 1440–1480 cm^{-1} and may be assigned to the C=N group and a thiadiazole ring deformation,[2,10] respectively. In contrast to derivatives of the 3*H*-[1,2,4]-thiadiazolo-[4,3-*a*]pyridine system,[11] all the members of these present systems, with the exception of 5,7-dimethyl-3-(2,6-dimethyl-4-pyrimidylimino)-3*H*-[1,2,4]thiadiazolo-[4,3-*c*]pyrimidine (**9**), showed no fluorescence and, in one or two instances, gave as yet unidentified photoproducts. In derivatives of the two fused-ring systems with exocyclic pyridyl substituents at the 3 position, the ultraviolet spectra consisted of four main bands centered at approximately 400, 330, 275, and 250 nm with the bands at 330 and 275 nm associated with the pyridine nucleus as in the 3*H*-[1,2,4]thiadiazolo[4,3-*a*]-pyridine system. Variation of substituents had predictable effects on the absorptions which are shown in Table I.

Representative nmr data for these compounds are described in Table II. In compounds containing the exocyclic 2-pyridylimino moiety, assignments for this substituent were made by analogy to related derivatives in the 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine system[2] and in those derivatives containing the thiadiazolo[4,3-*a*]pyrimidine nucleus, assignments are based on the downfield shift expected for protons adjacent to nitrogen and by comparison with derivatives of the *s*-triazolo[1,5-*a*]pyrimidine system.[12]

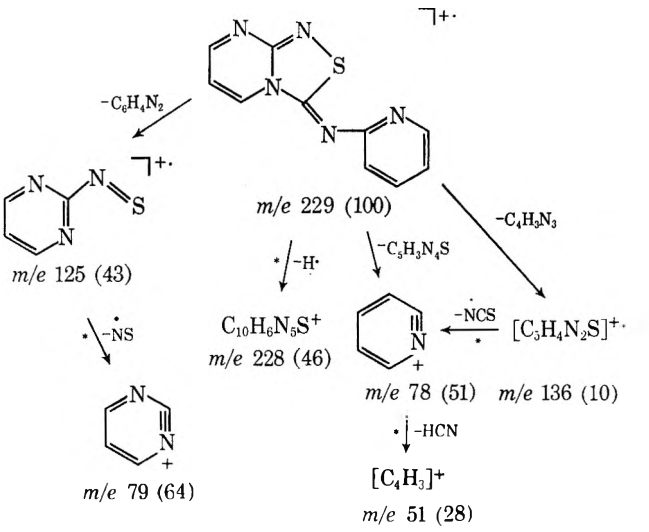
The stability of these compounds is reflected in the intensity of the molecular ions (frequently >90%) in their mass spectra. In all products derived from 2-aminopyrimidine and 2-aminopyrazine, a major fragmentation pathway of the bicyclic systems is the formation of a 2-pyrimidyl or 2-pyrazinylthionitroso ion. Other pathways are shown in Scheme I. In contrast, derivatives of the 3*H*-[1,2,4]thiadiazolo[4,3-*c*]pyrimidine system undergo a much more complicated fragmentation in which the only definitive feature is the loss of acetonitrile from the molecular ion. Similarly the 3*H*-[1,2,4]thiadiazolo[4,3-*b*]pyridazines lose a chlorine radical from the molecular ion in addition to the elimination of $C_6H_2ClN_6S$. In the latter case a $[C_3H_2Cl]^+$ ion, possibly a chlorocyclopropenium ion, is formed.

(10) J. Goerdeler and M. Budnowski, *Chem. Ber.*, **94**, 1682 (1961).

(11) K. T. Potts, H. H. Richtol, and R. Armbruster, *Anal. Chem.*, **43**, 1304 (1971).

(12) Y. Makisumi, H. Watanabe, and K. Tori, *Chem. Pharm. Bull.*, **12**, 204 (1964).

SCHEME I[a]



[a] Denotes metastable transition.

Experimental Section[13]

The following procedures illustrate the general methods employed.

2-Trichloromethylthioaminopyrimidine (**3**).—Perchloromethyl mercaptan (37.2 g) was suspended in a stirred solution of potassium carbonate (30 g), Alconox (1 g), water (600 ml), and crushed ice. A solution of 2-aminopyrimidine (19.0 g) in water (200 ml) was then added over 30 min. The precipitated product was collected, washed with water, and dried by suction. This was sufficiently pure for further use.

Method A. 3-(2-Pyridylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]-pyrimidine (**4**, R = 2-C_5H_4N).—A solution of 2-trichloromethylthioaminopyrimidine (4.0 g) in chloroform (100 ml) was added at room temperature to a stirred solution of 2-aminopyridine (1.54 g), triethylamine (5.0 g), and chloroform (250 ml). After stirring for 24 hr the solvent was removed from the reaction mixture, giving a brown solid which, after washing with methanol, crystallized from acetone as orange needles, 1.5 g (40%), mp 226–228° dec.

Method B. 5,7-Dimethyl-3-(2,6-dimethyl-4-pyrimidylimino)-3*H*-[1,2,4]thiadiazolo[4,3-c]pyrimidine (**9**).—A solution of perchloromethyl mercaptan (3.72 g) in chloroform (50 ml) was added over 30 min to a stirred solution of 4-amino-2,6-dimethylpyrimidine (4.93 g), triethylamine (8.1 g), and chloroform (150 ml). After stirring for 24 hr at room temperature, the reaction mixture was evaporated to dryness and the residue was leached with several portions of boiling benzene. The benzene was evaporated, and the residue was dissolved in a small volume of chloroform and then added to a column of Florisil (*ca.* 10 × 6.5 cm) and eluted with ethyl acetate. The resulting yellow solid crystallized from cyclohexane as matted, yellow needles, 1.9 g (33%), mp 182–184°.

Registry No.—**3**, 40899-18-1; **4** (R = 2-pyridyl), 40899-19-2; **4** (R = 4-methyl-2-pyridyl), 40899-20-5; **4** (R = 4,6-dimethyl-2-pyridyl), 40899-21-6; **4** (R = 5-chloro-2-pyridyl), 40899-22-7; **4** (R = 5-iodo-2-pyridyl), 40899-23-8; **4** (R = 2,5-dichlorophenyl), 40899-24-9; **4** (R = 3,4-dichlorophenyl), 40899-25-0; **4** (R = *p*-nitrophenyl), 40899-26-1; **4** (R = *m*-nitrophenyl), 40899-27-2; **9** (R = 2,6-dimethyl-4-pyrimidyl), 40899-23-3; **10** (R = 2-pyrazinyl), 40899-29-4; **12** (R = 6-chloro-3-pyridazinyl), 40899-30-7; **12** (R = 5-methyl-2-pyridyl), 40899-31-8; perchloromethylmercaptan, 75-70-7; 2-aminopyrimidine, 109-12-6; 2-aminopyridine, 504-29-0; 4-amino-2,6-dimethylpyrimidine, 461-98-3.

(13) All evaporations were done under reduced pressure using a rotatory evaporator. Spectral characterizations were performed with the following instrumentation: ir and uv spectra, Perkin-Elmer Model 337 and Cary Model 14 spectrophotometers; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer. Melting points were taken in capillaries and microanalyses were by Galbraith Laboratories, Inc., Knoxville, Tenn., and Instranal Laboratory, Inc., Rensselaer, N. Y. Plc was carried out on 20 × 20 nm plates using a 1-mm layer of silica gel PF 254 containing $CaSO_4$ with chloroform–ethyl acetate (80:20) as developing agent.

Bridged Azapolycyclic Alcohols from Intramolecular Epoxide Ring Openings by Amides

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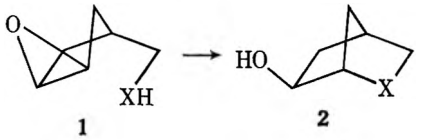
Received May 2, 1973

An epoxide ring opening by an intramolecular nucleophilic attack of an amide group was utilized to synthesize 2-azanorbornan-6-ols and 2-azaadamantan-4-ols. The spectral identification of these compounds is described.

In the courses of our studies of heteronorbornanes[3,4] and 2-adamantyl derivatives[5] we were led to devise synthetic routes to the 2-aza analogs of these two types of bridged polycyclic skeleta. The main requisite in both cases lay in the versatility of the synthetic method with regard to substituent variation on the ring-incorporated nitrogen. Fortunately, a single reaction type sufficed as the culminating step in the syntheses of both 2-azanorborn-6-yl derivatives and 2-azaadamant-4-yl derivatives. The reaction, a ring closure effected through an intramolecular epoxide ring opening, had been applied previously in the syntheses of 2-oxanorbornan-6-ol[3] (**2a**) and 2-thianorbornan-6-ol[6] (**2b**) from *trans*-3,4-epoxycyclopentylmethyl alcohol (**1a**) and thiol (**1b**), respectively. Interestingly, it failed completely for syntheses of the amine analogs **2c**, owing to an inability to epoxidize the requisite olefins for preparation of **1c**.

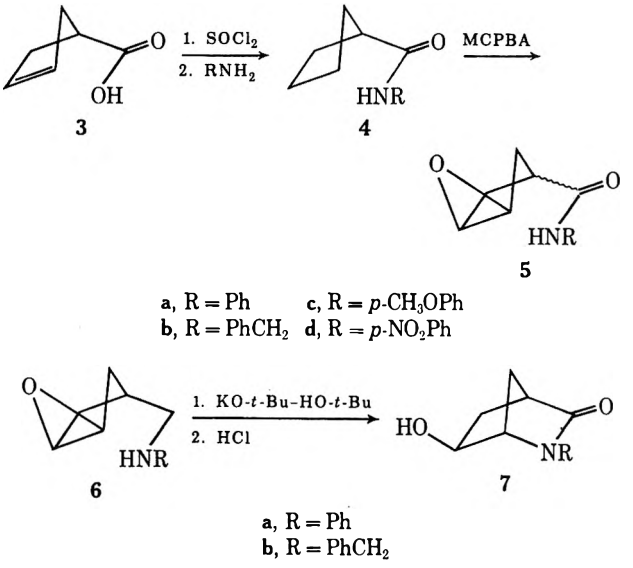


1 **2**

a, X = O
b, X = S
c, X = NR

As the latter difficulty could only be attributed to the amine nitrogen, several epoxy amides (**5**) were prepared by conventional procedures from Δ^3-cyclopentenecarboxylic acid[7] (**3**) (Scheme I). Separations of the trans epoxides (**6**) were accomplished by recrystallization. Cyclizations of **6a** and **6b** were smoothly effected by potassium *tert*-butoxide in *tert*-butyl alcohol at reflux. Infrared analyses of the crude products showed the disappearance of epoxide absorptions, appearance of hydroxyl absorptions, and a shift of the amide C=O stretching frequency to the higher wavenumber characteristic of the lactam.[8] The nmr spectra of the purified lactams substantiated the structural assignments, as did those of subsequent conversion products (Table I).

SCHEME I



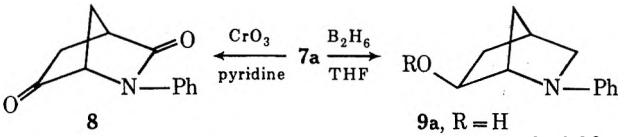
3 **4** **5**

a, R = Ph **c**, R = *p*-CH_3OPh
b, R = $PhCH_2$ **d**, R = *p*-NO_2Ph

6 **7**

a, R = Ph
b, R = $PhCH_2$

For further characterization the *N*-phenyl hydroxylactam **7a** was converted to its corresponding ketone **8** by chromium trioxide–pyridine oxidation. In addition, **7a** underwent facile reduction with a diborane–tetrahydrofuran mixture to afford crystalline amino alcohol **9a**, which along with its *p*-nitrobenzoate (**9b**) and acetate (**9c**) derivatives, was structurally identified on the basis of its well-defined nmr spectrum (Table I).



8

9a, R = H
b, R = *p*-NO_2PhCO
c, R = CH_3CO

The preparation of **9a** confirmed the viability of the synthetic technique and indicated its having met the previously stated criterion as a general method for preparation of 2-substituted 2-azanorbornan-6-ols. This success led to our investigation of the ring closure method for preparation of azaadamantanols of similar structural relationship between hydroxyl and ring nitrogen.

N-endo-Bicyclo[3.3.1]non-6-en-3-ylbenzamide (**11**) was prepared from the related carboxylic acid[9] **10** by a conventional series of reactions[10] (see Scheme II).

(1) (a) Taken in part from the Ph.D. thesis of R. J. Schultz, Brown University, 1971; (b) Taken in part from the Ph.D. thesis of W. H. Staas, Brown University, 1973.

(2) Alfred P. Sloan Fellow, 1973–1975.

(3) L. A. Spurlock and R. G. Fayter, Jr., *J. Amer. Chem. Soc.*, **94**, 2707 (1972).

(4) L. A. Spurlock and R. G. Fayter, Jr., Abstracts, 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, ORGN 108; L. A. Spurlock, R. D. Gleim, and R. J. Schultz, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971, ORGN 133.

(5) L. A. Spurlock and K. P. Clark, *J. Amer. Chem. Soc.*, **94**, 5349 (1972); **92**, 3289 (1970).

(6) C. R. Johnson, J. E. Keiser, and J. C. Sharp, *J. Org. Chem.*, **34**, 860 (1969).

(7) K. C. Murdock and R. B. Angier, *J. Org. Chem.*, **27**, 2395 (1962).

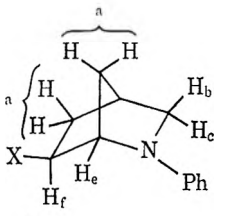
(8) The cyclizations of *trans*-**5c** and **5d** gave similar apparent results; however, the crude products in these cases were characterized only by their infrared spectra and no further attempt was made to utilize these materials.

(9) T. Sasaki, S. Eguchi, and T. Toru, *J. Org. Chem.*, **35**, 4109 (1970).

(10) The reaction sequence proceeded from **10** *via* diazomethane esterification, conversion to the hydrazide, Curtius rearrangement to the endo amine, and benzoylation to give **11**. Experimental details will be given in a subsequent publication.

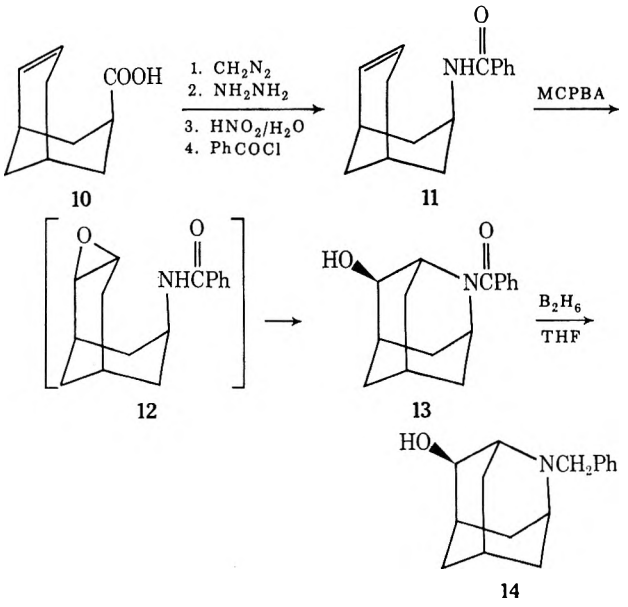
TABLE I

CHEMICAL SHIFTS (δ) OF *N*-PHENYL-*exo*-6-SUBSTITUTED 2-AZANORBORNYL DERIVATIVES



Proton	7a	9a
H_a	1.43–2.36 (m)	1.15–2.00 (m)
H_b	2.80 (m)	2.53 (br s)
H_c		2.53 (d)
H_d		3.28 (d tr)
H_e	4.23 (br s)	3.87 (br s)
H_f	4.29 (dd)	3.86 (dd)
	9b	**9c**
H_a	1.82, 1.98 (br s)	1.70, 1.81 (br s)
H_b	3.72 (m)	2.62 (d)
H_c	2.73 (d)	2.62 (d)
H_d	3.45 (d tr)	3.38 (dq)
H_e	4.31 (br s)	4.13 (br s)
H_f	5.05 (dd)	4.77 (dd)

SCHEME II



Treatment of the olefin **11** with *m*-chloroperbenzoic acid in methylene chloride at room temperature (the procedure utilized in preparation of **5**) afforded a product in 80% yield which, on the bases of its infrared and nmr spectra, was assigned the ring-closed structure, *N*-benzoyl-2-azadamantan-*anti*-4-ol (**13**). This unexpectedly facile closure of epoxyamide **12** apparently resulted from the unusual proximity of the amide nitrogen to the back side of the epoxide-bearing ring carbon.[11] Quite happily we were thus provided with a highly efficient means of obtaining the desired synthetic goal of an azaadamantanol with possibilities (hydrolysis and alkylation or direct reduction) for easy substituent variation at the nitrogen. One of these variants, the *N*-benzylazaadamantanol **14**, was, in fact, achieved by reduction of **13** with diborane in tetrahydrofuran. Its structure could likewise be confirmed by infrared and nmr spectra.

The further application of this technique to heteropolycyclic systems will be reported later, as will the developments of the azapolycyclic derivatives already prepared.

(11) This is one of several examples which we have observed of unusually enhanced reactivity at the former double bond sites of this endo-substituted bicyclic ring system. All are seemingly related to proximity effects.

Experimental Section[12]

Δ³-Cyclopentenecarboxylic Acid (3).—The procedure of Murdock and Angier[7] was utilized to convert 156 g (1.25 mol) of *cis*-1,4-dichloro-2-butene and 200 g (1.25 mol) of diethyl malonate to 24.75 g of pure **3**, bp 98–99° (7.5 mm) [lit.[7] bp 83–84° (2 mm)].

Δ³-Cyclopentenecarbonyl Chloride.—To 67.2 g (0.600 mol) of **3** being stirred and cooled with an ice bath was added dropwise 55 ml of thionyl chloride. The reaction mixture was then stirred overnight at room temperature. The crude mixture was distilled at 51 mm, giving 76.9 g (98.2%) of the desired product, bp 79–80° [lit.[7] bp 95–96° (55 mm)].

General Procedure for Preparation of Amides.—A solution of Δ³-cyclopentenecarbonyl chloride (0.025 mol) dissolved in 50 ml of anhydrous ether was added dropwise to a solution of 0.05 mol of primary amine dissolved in 50 ml of ether being stirred at 5°. Upon completion of the addition, the reaction mixture was stirred at room temperature overnight. The amine hydrochloride was removed by filtration and thoroughly washed with ether. The combined ether solutions were dried over magnesium sulfate and concentrated. In this fashion the following secondary amides were prepared, with solvents for recrystallization and yields indicated: *tert*-butyl, mp 127.5–128.5° (78.8%); phenyl, **4a**, mp 139.5–140.5° from $CHCl_3$–pentane (75.8%) (lit.[7] mp 140°); benzyl, **4b**, mp 112–113° from CH_2Cl_2–pentane (77.3%); *p*-nitrophenyl, **4d**, mp 121–123° from $CHCl_3$ (74.7%); and *p*-methoxyphenyl, **4c**, mp 138–140° (79.4%).

***cis*- and *trans*-3,4-Epoxycyclopentenecarboxamides (5).**—In a typical procedure, 0.341 mol of amide **4** was dissolved in 725 ml of chloroform and stirred at 5°. To this solution was added dropwise 83.1 g of 85% *m*-chloroperbenzoic acid dissolved in 950 ml of chloroform. After the addition was complete, the mixture was allowed to come to room temperature and was stirred overnight. The excess peracid was destroyed by the addition of 10% sodium sulfite solution and the reaction mixture was filtered. The chloroform solution was washed with 5% sodium hydroxide solution, dried over magnesium sulfate, and concentrated to give the crude epoxide mixture.

In the case of the *p*-nitrophenyl and *p*-methoxyphenyl compounds, only partial separation of isomers was achieved. Trituration of the crude *p*-nitrophenyl reaction product with chloroform left a yellow, crystalline solid, mp 225–230° (53.1%). Addition of pentane to the chloroform solution deposited a pale yellow, fluffy solid, mp 161–168° (32.3%). The same procedure was applied to the crude *p*-methoxyphenyl product, giving a fluffy white, chloroform-insoluble solid, mp 182–185° (32.5%). From the chloroform solution was obtained a light tan solid, mp 142–145° (50.8%).

The crude material from epoxidation of the phenyl amide **4a** was completely soluble in chloroform but upon addition of pentane deposited a 55.4% yield of the trans epoxide **6a** as a white, crystalline solid: mp 169–170°; nmr (DMSO-d_6) δ (TMS) 1.52–2.89 (5 H, m), 3.56 (1 H, s), 6.70–7.78 (5 H, m). The filtrate from **6a** was concentrated and the residue was recrystallized from ether–pentane, giving the cis epoxide as a fluffy, white solid: mp 112–114° (35.8%); nmr ($CDCl_3$) δ (TMS) 1.72–3.23 (5 H, m), 3.62 (2 H, s), 6.72–7.75 (6 H, m).

Treating a chloroform solution of the crude *N*-benzyl epoxide mixture with pentane gave, on cooling, a 45.7% yield of the trans isomer **6b** as a white solid: mp 140.0–141.5°; ir (Nujol) 3275, 1640, 1540, 1218, 1050, and 845 cm^{-1}; nmr ($CDCl_3$) δ (TMS) 1.78–2.50 (5 H, m), 3.40 (2 H, s), 4.28 (2 H, d), 6.42 (1 H, br s), 7.15 (5 H, s). Concentration of the filtrate gave impure cis epoxide as a yellow oil, ir (film) 3300, 1650, 1545, and 840 cm^{-1}.

(12) Infrared spectra were determined on a Perkin-Elmer Model 337 grating infrared spectrometer using sodium chloride optics. Nmr determinations were carried out on a Varian Associates A-60A spectrometer; approximately 20% solutions in a deuterated solvent ($CDCl_3$ or DMSO-d_6) were employed with tetramethylsilane as the internal standard. Analyses were carried out by Micro-Analysis, Inc., Wilmington, Del.

N-Phenyl-*exo*-6-hydroxy-2-azabicyclo[2.2.1]heptan-3-one (7a).—To a hot solution of 14.8 g (0.378 g-atom) of potassium in 1150 ml of *tert*-butyl alcohol was added in small portions over a period of 30 min 38.4 g (0.198 mol) of 6a. The resulting orange solution was heated at reflux for 14 hr, after which time approximately 700 ml of *tert*-butyl alcohol was removed by distillation. The cooled solution was acidified with concentrated hydrochloric acid (39 ml) and filtered. The filtrate was concentrated to approximately 200 ml and then dissolved in 300 ml of chloroform. The chloroform solution was washed seven times with 100-ml portions of water and once with saturated sodium chloride solution, dried, and concentrated, giving 30.5 g (79.4%) of crude product as a dark tan solid. An analytical sample of 7a was obtained after five recrystallizations from absolute ethanol: mp 120.5–122.0°; ir ($CHCl_3$) 3440, 1700, 1600, 1500, 1280, 1160, 1078, 1068, 990, and 947 cm^{-1}; nmr ($CDCl_3$) δ (TMS) 1.43–2.36 (4 H, m), 2.80 (1 H, m), 3.97 (1 H, br s), 4.23 (1 H, br s), 4.29 (1 H, dd), and 5.88–7.64 (5 H, m).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.03; H, 6.54; N, 6.92.

N-Benzyl-*exo*-6-hydroxy-2-azabicyclo[2.2.1]heptan-3-one (7b).—The preparation was carried out in a similar fashion to that of 7a. The trans epoxy amide 6b, 29.6 g (0.136 mol), was treated with a hot solution of 10.67 g (0.273 g-atom) of potassium in 850 ml of *tert*-butyl alcohol. On work-up, 26.7 g of a dark oil was obtained. Crystallization was accomplished by trituration of the oil with ether. In this fashion a light tan solid was obtained: mp 105–107°; ir (Nujol) 3350, 1680, 1410, 1225, 1075, 970, 750, and 700 cm^{-1}; nmr ($CDCl_3$) δ (TMS) 1.28–2.22 (4 H, m), 2.61 (1 H, m), 3.46 (1 H, br s), 3.70–4.22 (3 H, m), 4.47 (1 H, d), 7.13 (5 H, s).

N-Phenyl-*exo*-6-hydroxy-2-azabicyclo[2.2.2]heptane (9a).—Treatment of 14.21 g (0.07 mol) of crude 7a dissolved in 75 ml of tetrahydrofuran with 117 ml of approximately 1 *M* borane in tetrahydrofuran, utilizing the reductive method of Brown and Heim,[13] gave 17 g of crude material as an orange oil. A portion of the crude product was distilled at 124.5–127.0° (0.1 mm), affording the amino alcohol as a colorless oil which slowly solidified to a white, waxy solid, mp 80.5–83.0°. Four recrystallizations from ether–pentane gave pure 9a as fluffy, white needles: mp 85.0–85.5°; ir ($CHCl_3$) 3650, 3465, 1600, 1500, 1146, 1080, 1010, 920, and 690 cm^{-1}; nmr ($CDCl_3$) δ (TMS) 1.15–2.00 (4 H, m), 2.53 (1 H, br s), 2.53 (1 H, d), 2.70 (1 H, s), 3.28 (1 H, d tr), 3.86 (1 H, dd), 3.87 (1 H, br s), 6.33–7.38 (5 H, m).

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.16; 7.99; N, 7.40. Found: C, 75.98; H, 7.96; N, 7.40.

The *p*-nitrobenzoate 9b was recrystallized from ether, giving red needles: mp 141–142.5°; ir ($CDCl_3$) 1720, 1600, 1525, 1280, 1120, 1105, 1018, and 1000 cm^{-1}; nmr ($CDCl_3$) δ 1.82 (2 H, br s), 1.98 (2 H, br s), 2.73 (1 H, m), 2.73 (1 H, d), 3.45 (1 H, d tr), 4.31 (1 H, br s), 5.05 (1 H, dd), 6.52–7.44 (5 H, m), 8.25 (4 H, s).

Anal. Calcd. for $C_{19}H_{18}N_2O_4$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.45; H, 5.44; N, 8.43.

The acetate 9c was obtained as a colorless oil: bp 126–127° (0.1 mm); ir (film) 1730, 1590, 1370, 1240, 1140, 1045, and 740 cm^{-1}; nmr ($CDCl_3$) δ (TMS) 1.70 (2 H, br s), 1.81 (2 H, br s), 2.00 (3 H, s), 2.62 (1 H, d), 2.62 (1 H, d), 2.62 (1 H, d), 3.38 (1 H, dq), 4.13 (1 H, br s), 4.77 (1 H, dd), 6.48–7.38 (5 H, m.).

N-Phenyl-2-azabicyclo[2.2.1]heptane-3,6-dione (8).—The amino alcohol 7a, 2.03 g (0.01 mol), was oxidized with chromium trioxide and pyridine in methylene chloride according to the procedure of Ratcliffe and Rodehorst.[14] The crude product was recrystallized from ether, giving 1.493 g (74.3%) of pure 8 as white needles: mp 105–106°; ir ($CHCl_3$) 1770 1720, 1600, 1500, 1365, 1291, 1127, 1100, and 980 cm^{-1}; nmr ($CDCl_3$) δ (TMS) 1.68–2.63 (4 H, m), 3.05 (1 H, m), 4.22 (1 H, dd), 6.88–7.62 (5 H, m).

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.41; H, 5.74; 6.93.

N-Benzoyl-2-azaadamantan-4-ol (13).—To 4.04 g (0.02 mol) of 85% *m*-chloroperbenzoic acid dissolved in 40 ml of methylene chloride was added dropwise a solution of 4.8 g (0.02 mol) of 11[10] dissolved in 40 ml of methylene chloride. The temperature was maintained below 25° during the addition. Afterward, the solution was allowed to stir at room temperature overnight. The excess oxidizing agent was destroyed by washing with 10% sodium bisulfite solution and the resulting solution was washed with saturated sodium bicarbonate solution and then with water until neutral. The solution was dried and concentrated to give 5.1 g of colorless oil which crystallized upon treatment with a single drop of ethanol. The resultant oily solid was slurried with hexane and filtered to give 4.2 g (82.5%) of 13 as a white, crystalline solid. An analytical sample was prepared by recrystallization from benzene–hexane: mp 143–145°; ir ($CHCl_3$) 3320, 2930, 2850, 1590, 1570, 1445, 1375, 1080, 1025, 970, 920, 790, 735, and 700 cm^{-1}; nmr ($CDCl_3$) δ (TMS) 1.18–2.54 (10 H, m), 3.45 (1 H, s), 3.80 (2 H, m), 4.75 (1 H, m), 7.34 (5 H, s).

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.85; H, 7.29; N, 5.46.

N-Benzyl-2-azaadamantan-4-ol (14).—Reduction of 13 was effected using the method of Brown and Heim.[13] A 1.28-g (0.005 mol) sample of 13 in 25 ml of tetrahydrofuran was treated with 10 ml of an approximately 1 *M* solution of diborane in tetrahydrofuran. Standard work-up gave 1.1 g (90%) of 14 as a white, crystalline solid. An analytical sample was prepared by recrystallization from cyclohexane–pentane: mp 94.5–96°; ir (mull) 3340, 2930, 2850, 1500, 1455, 1360, 1150, 1080, 1050, 1035, 1000, 740, and 700 cm^{-1}; nmr ($CDCl_3$) δ (TMS) 1.18–2.33 (11 H, m), 2.67 (2 H, m), 3.81 (2H, s), 4.0 (1H, m), 7.24 (5H, br s).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.69; H, 8.58; N, 5.61.

Registry No.—4 (R = *t*-Bu), 40810-34-2; 4a, 7686-79-5; 4b, 40810-36-4; 4c, 40810-37-5; 4d, 40810-38-6; *cis*-5c, 40810-39-7; *trans*-5c, 40810-40-0; *cis*-5d, 40810-41-1; *trans*-5d, 40810-42-2; 6a, 40810-43-3; *cis*-6a, 40810-44-4; 6b, 40810-45-5; *cis*-6b, 40810-46-6; 7a, 40810-47-7; 7b, 38318-60-4; 8, 40810-49-9; 9a, 40810-50-2; 9b, 40810-51-3; 9c, 40810-52-4; 11, 40923-03-3; 13, 40810-53-5; 14, 40810-54-6; Δ^3-cyclopentenecarbonyl chloride, 3744-80-7.

(13) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964).

(14) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

The Boron Trifluoride Catalyzed Cycloaddition of Iminourethanes with Cyclic Conjugated Olefins. An Examination of Reaction Stereochemistry

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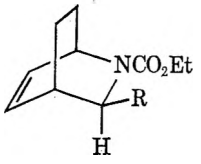
The reaction of formaldehyde bisurethane with five-, seven-, and eight-membered-ring conjugated dienes and cycloheptatriene has been investigated. Bicyclic urethanes are obtained with the seven-membered-ring conjugated systems only; substituted dienes result from both seven- and eight-membered-ring dienes. Reaction products are consistent with a mechanism involving attack by diene on an acid-complexed iminourethane. The stereochemistry of phenyl-substituted bicyclic urethanes synthesized from cycloheptatriene and cyclohepta-1,3-diene using benzaldehyde bisurethane has been determined using nmr with the aid of decoupling experiments. The stereochemical results have been rationalized on the basis of stepwise cycloadditions *via* (*E*)-iminourethanes.

The acid-catalyzed cycloaddition reaction between cyclohexa-1,3-diene and iminocarbamates offers a convenient synthetic route to 3-substituted 5,6-dehydroisoquinuclidines **1**. We have recently reported[1a] on the stereochemical outcome of the synthesis of 3-aryl- and 3-acetyl-5,6-dehydroisoquinuclidines **1b** and **1c** in which predominant formation of the less

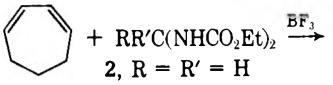


1a, R = H
b, R = Ph
c, R = $COCH_3$

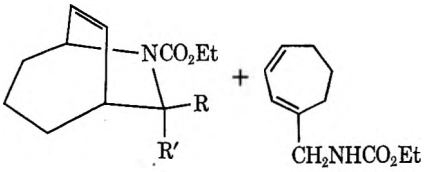
stable 3-exo substituted isomers was found to occur.[1b] We here report an extension of these stereochemical studies to the azabicyclics formed from cyclohepta-1,3-diene and cycloheptatriene, and our observations on the course of the reaction of methylenebisurethane with cyclopentadiene and cyclooctadiene.

Reaction with Cyclohepta-1,3-diene.—Methylenebisurethane (**2**) reacts in the presence of boron trifluoride with cyclohepta-1,3-diene[2] to form *N*-carbethoxy-6-azabicyclo[3.2.2]oct-8-ene (**4**) and the addition–abstraction product **5**. Of importance for stereochemical studies on the reaction of substituted iminourethanes with cyclohepta-1,3-diene are the separate nmr (acetone-d_6) resonances (Table I) for $H_{7\text{-syn}}$ (δ 3.18) and $H_{7\text{-anti}}$ (δ 3.52) and the unequal couplings $J_{1,7\text{-syn}}$ = 3.2 Hz, $J_{1,7\text{-anti}}$ = 1.6 Hz of these hydrogens with the adjacent bridgehead hydrogen H_1. Assignment of the upfield position to the $H_{7\text{-syn}}$ relative to $H_{7\text{-anti}}$ proton can be made on the basis of a previously observed[1a] shielding of the analogous syn proton in the nmr spectrum of *N*-carbethoxy-5,6-dehydroisoquinuclidine (**1a**). The larger vicinal coupling $J_{1,7\text{-syn}}$ is as expected based on the smaller dihedral angle relationship[3] for $H_{7\text{-syn}}$ and H_1 as noted in Dreiding models.

Reaction of benzalbisurethane and cyclohepta-1,3-diene afforded a mixture of the epimeric syn (**6**) and anti (**7**) phenyl adducts for which the nmr spectra



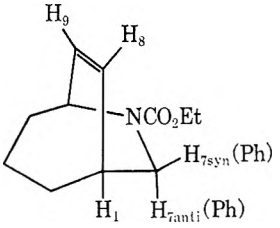
2, R = R′ = H
3, R = H; R′ = Ph



4, R = R′ = H
6, R = Ph; R′ = H
7, R = H; R′ = Ph

5

TABLE I
100-MHz PROTON NMR PARAMETERS FOR CYCLOHEPTA-1,3-DIENE ADDUCTS



Compd	Absorption	Chemical shift and description
4[a]	$H_{7\text{-syn}}$	3.18 dd ($J_{1,7\text{-syn}}$ = 3.2, $J_{7\text{-syn},7\text{-anti}}$ = 11.2 Hz)
	$H_{7\text{-anti}}$	3.52 dd ($J_{1,7\text{-anti}}$ = 1.6 Hz)
	$H_{8,9}$	6.16 m
6 (syn Ph)[b]	$H_{7\text{-anti}}$	4.88 d ($J_{7,1}$ = 1.6 Hz)
	H_8	5.80 m
	H_9	6.18 m
7 (anti Ph)[b]	$H_{7\text{-syn}}$	4.62 d ($J_{7,1}$ = 4.4 Hz)
	$H_{8,9}$	6.18 m

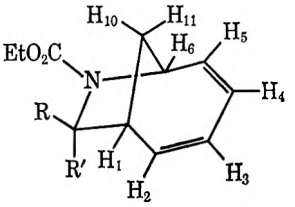
[a] Solvent, acetone-d_6. [b] Solvent, $CDCl_3$.

($CDCl_3$) are shown in Table I. Notably, H_8 in the isomer **6** with phenyl syn to the olefinic bond was shielded by 0.38 ppm relative to H_9. This shielding effect by the phenyl substituent on the proximate olefinic hydrogen was noted previously[1a] in the spectra of *syn*-3-phenyl-*N*-carbethoxy-5,6-dehydroisoquinuclidine (**1b**). Spin-decoupling experiments confirmed a 0.26-ppm upfield position for $H_{7\text{-syn}}$ (δ 4.62) of the anti-phenyl isomer **7** relative to $H_{7\text{-anti}}$ (δ 4.88) of the syn-phenyl isomer **6**. As expected from dihedral angle relationships the coupling $J_{1,7\text{-syn}}$ = 4.4 Hz in

(1) (a) G. Krow and R. Rodebaugh, *J. Org. Magn. Resonance*, **5**, 73 (1973); (b) G. Krow, R. Rodebaugh, R. Carmosin, W. Figures, H. Pannella, G. DeVicaris, and M. Grippi, *J. Amer. Chem. Soc.*, **95**, 5273 (1973); (c) H. Harter and S. Liisberg, *Acta Chem. Scand.*, **22**, 2685 (1968); (d) M. Cava, C. Wilkins, D. Dalton, and K. Bessho, *J. Org. Chem.*, **30**, 3772 (1965).
(2) J. D. Hobson and W. D. Riddell, *Chem. Commun.*, 1180 (1968).
(3) P. Laszlo and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964).

TABLE II

100-MHz PROTON NMR SPECTRUM OF THE METHYLENEURETHANE–CYCLOHEPTATRIENE ADDUCTS[a]



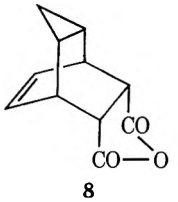
10, R = H_8; R′ = H_9
11, R = Ph; R′ = H_9
12, R = H_9; R′ = Ph

	10		11		12	
Absorption	δ	Description	δ	Description	δ	Description
H_1	2.82	q[b]	2.62	m[j]	3.16	q[l]
H_2	6.02	br	6.16	m	5.18	m[m]
H_3, H_4	5.70	m[c]	5.74	m	5.74	m
H_5	6.02	br[d]	6.16	m[d]	6.16	m
H_6	4.30	t[e]	4.57	t[k]	4.57	t[n]
H_8	3.40	dd[f]			5.08	d
					(5.20)[i]	
H_9	3.70	d	5.26	s		
			(5.20)[i]			
H_{10}	2.40	dt[g,h]	2.45	m[g]	2.45	m[g]
H_{11}	2.05	d[h]	1.92	d	2.10	d
OCH_2	4.00	br[i]	3.94	br[i]	3.94	br[i]
CH_3	1.18	t	0.90	t	0.90	t
	(1.20)[i]		(1.20)[i]		(1.20)[i]	
Ph			7.15	m	7.15	m

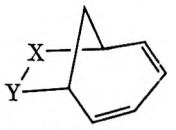
[a] Solvent, acetone-d_6. [b] $J_{1,10} \cong J_{1,8} \cong J_{1,2} = 6.0$ Hz. [c] $J_{2,3} = 12$ Hz, $J_{3,5} = 3.5$ Hz. [d] Overlaps with H_2. [e] $J_{5,6} \cong J_{6,10} = 7.5$ Hz. [f] $J_{8,9} = 10$ Hz. [g] $J_{10,11} = 12$ Hz. [h] Coupling pattern is observed more clearly in $CDCl_3$. [i] Separate patterns result from separate urethane conformations. [j] $J_{1,9} \cong 0$ Hz, $J_{1,2} = J_{1,10} = 5$ Hz. [k] $J_{5,6} = 7.0$ Hz, $J_{6,10} = 5.5$ Hz. [l] $J_{1,8} = 6$ Hz, $J_{1,2} = J_{1,10} = 7.0$ Hz. [m] $J_{2,3} = 11.5$ Hz. [n] $J_{5,6} = J_{6,10} = 7.0$ Hz.

7 was greater than $J_{1,7\text{-anti}} = 1.6$ Hz of 6. The ratio of syn:anti phenyl isomers was conveniently determined as 1.0 by comparing the integrated area of H_8 of the syn-phenyl isomer with the remaining olefinics ($H_{8,9}$ of the anti-phenyl isomer and H_9 of the syn-phenyl isomer) or with $H_{7\text{-syn}}$ of the anti-phenyl isomer 7.

Reaction with Cycloheptatriene.—In principle reaction of methylenebisurethane with cycloheptatriene might give rise to a number of unusual azabicyclics. Cycloheptatriene forms [4 + 2] adduct **8** by reacting with maleic anhydride *via* the norcaradiene valence tautomer,[4] while the [6 + 2] adducts **9** are found to



8



9a, X = Y = O
b, X = NSOCl; Y = CO
c, X = NPh, Y = O

result from additions of heteroenes, such as chlorosulfonyl isocyanate,[5] nitrosobenzene,[6] and singlet oxygen.[7]

When cycloheptatriene was treated in the usual manner with methylenebisurethane, the single bicyclic adduct **10** was obtained in moderate yield. The structure of **10** can be determined uniquely from the spectral parameters [uv (CH_3CN) λ_{max} 264 mμ (ε 3760), 240 (3320); ir (CCl_4) 1690 cm^{-1}] and the nmr spectrum (Table II) in combination with the spin-decoupling technique.

Irradiation of H_9 of **10** resulted in a narrowing of the peak width at half-height of H_{11} from 6 to 4 Hz, indicating slight W-plan coupling. The lack of observable coupling $J_{1,11} \cong J_{6,11} \cong J_{9,1} \cong 0$ Hz results from nearly 90° dihedral angle relationships for each of these hydrogen pairs, as can be seen on Dreiding models.

Conformational effects are associated with the urethane functionality, which can have the ethoxyl syn or anti to the adjacent methylene group when in the planar amide conformation,[8] The result is a broadening of the ethoxyl methylene resonance and a separate set of triplet resonances. When $CDCl_3$ was used as solvent, the conformational effect of the urethane resulted in observation of two distinct but partially overlapping resonance patterns for H_6, H_8, and H_9, the protons on carbon adjacent to the nitrogen functionality.

Benzalbisurethane **3** and cycloheptatriene, reacted in the usual manner, afforded benzylurethane **14** (16%) and an epimeric mixture of [6 + 2] adducts **11** and **12** (10%, 80:20, **11**:**12**). The adducts **11** and

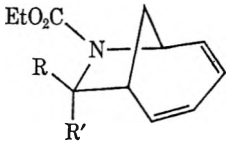
(4) (a) A. S. Onishchenko, "Diene Synthesis," Davey, New York, N. Y., 1964, pp 370–376. (b) D. Bellus, G. Helferich, and C. D. Weiss, *Helv. Chim. Acta*, **54**, 463 (1971). Small amounts of [6 + 2] products occasionally arise, possibly *via* a diradical pathway. (c) H. Ishitobi, H. Tanida, K. Tori, and T. Tsuji, *Bull. Chem. Soc. Jap.*, **44**, 2993 (1971).

(5) (a) E. J. Moriconi, C. F. Hummel, and J. F. Kelly, *Tetrahedron Lett.*, 5325 (1969); (b) J. R. Malpass, *Chem. Commun.*, 1246 (1972).

(6) P. Burns and W. A. Waters, *J. Chem. Soc. C*, 27 (1969).

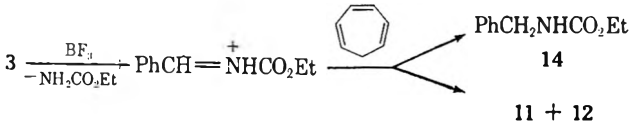
(7) A. S. Kende and J. Y. C. Chu, *Tetrahedron Lett.*, 4837 (1970).

(8) (a) P. T. Inglefield and S. Kaplan, *Can. J. Chem.*, **50**, 1594 (1972); (b) S. VanderWerf and J. Engberts, *Recl. Trav. Chim. Pays-Bas*, **90**, 663 (1971).



10, R = R′ = H
11, R = Ph; R′ = H
12, R = H; R′ = Ph

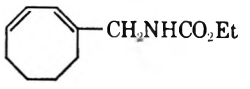
12 were characterized by uv (EtOH), λ_{max} 254 mμ (ε 3900), ir (CCl_4), 1695 cm^{-1}, and their individual



nmr (acetone-d_6) patterns (Table II). Notably in **12** the syn-phenyl group causes an upfield shift for the proximate olefinic proton H_2 of 0.98 ppm relative to the remaining olefinic protons, a shift which has also been qualitatively diagnostic for adducts **1b** from cyclohexa-1,3-diene and **6** from cycloheptа-1,3-diene (*vide supra*) where phenyl is syn to the olefinic linkage. In addition a downfield shift of 0.54 ppm for H_1 of the syn-phenyl isomer **12** relative to the corresponding H_1 proton in the anti-phenyl isomer **11** was observed. This latter shift readily allowed the determination of isomer ratios from the mixture of the two isomers **11** and **12**.

Conformational effects associated with restricted rotation of the urethane functionality and possibly restricted phenyl rotation resulted in broadening of the ethoxyl methylene resonances, and observation of two separate triplet resonances, two singlets for H_9 of **11** and two doublets for H_8 of **12**. The magnitudes of the separate peaks were strongly effected upon changing the solvent from acetone-d_6 to $CDCl_3$. The appearance of H_6, the other proton on carbon adjacent to nitrogen, was not perturbed in either of the isomers **11** or **12** in the solvents studied.

Reaction with Cycloocta-1,3-diene and Cyclopenta-1,3-diene.—The reaction of dienophiles with cycloocta-1,3-diene has not been found to lead to the formation of bicyclic products.[4a] Similarly, when methylenebisurethane was treated with cycloocta-1,3-diene under the usual conditions, the diene **15** (27%), whose



15

structure follows from mechanistic and spectral considerations, was obtained as the only product formed from 1:1 methyleneurethane–diene addition. Although cyclopentadiene reacts readily with a number of dienophilic imines to form azabicyclic molecules,[9,10] reaction of methylenebisurethane with cyclopentadiene under the present acid-catalyzed conditions did not lead to the isolation of 1:1 methyleneurethane–diene adducts.

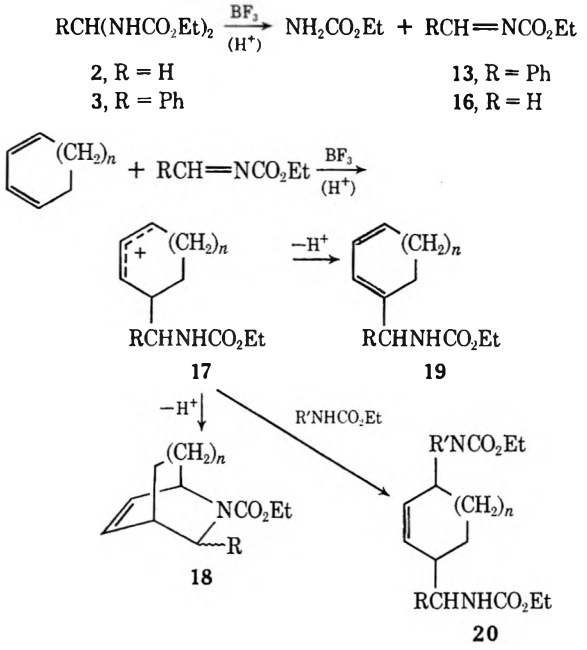
(9) (a) J. Biehler and J. Fleury, *J. Heterocycl. Chem.*, **8**, 431 (1971); (b) G. Kresze and R. Albrecht, *Chem. Ber.*, **97**, 490 (1964).

(10) G. Krow, R. Rodebaugh, J. Marakowski, and K. Ramey, *Tetrahedron Lett.*, 1899 (1973).

Conclusions

In a previous study[1b] of the reaction of cyclohexa-1,3-diene with alkylidenebisurethanes it was suggested that bicyclic urethane formation was the likely result of a stepwise process (Scheme I) involving acid-com-

SCHEME I



plexed imines.[11] Initial diene addition to the carbon of an acid-complexed iminourethane can form an allylic cation species **17**, which upon intramolecular attack by urethane nitrogen and loss of a proton leads to bicyclic product **18**. Alternatively, the allylic cation can lose a proton to generate a substituted cyclic diene system **19** or be attacked by various urethane species in solution to form less volatile diurethanes **20**. In the present work we have focused our attention on the more volatile monourethane species **18** and **19**.

The present study indicates that formation of substituted dienes **19** assumes importance to a small extent for reactions of cyclohepta-1,3-diene and to a greater degree for reaction of cycloocta-1,3-diene. For the latter, the failure to observe bicyclic urethanes **18** is likely due to conformational strain in assuming the requisite boatlike geometry[12] for intramolecular ring closure of the allylic cation **17**.

The stereochemical results for synthesis of phenyl-substituted azabicyclics are presented in Table III.

TABLE III
STEREOCHEMICAL OUTCOME OF REACTIONS OF CYCLIC DIENES WITH BENZALBISURETHANE[a]

Diene	Structure	% anti phenyl[b]
Cyclohexa-1,3-diene	**22** and **23**	80
Cycloheptа-1,3-diene	**6** and **7**	50
Cycloheptatriene	**11** and **12**	79

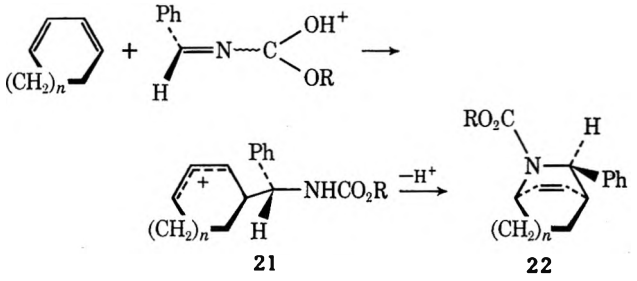
[a] Benzene solvent, BF_3 catalyst. [b] Anti relative to the olefinic bridge.

(11) (a) G. Krow, H. Pannella, and W. Figures, *J. Chem. Eng. Data*, **17**, 116 (1972); (b) T. Sasaki, S. Eguchi, M. Sugimoto, and F. Hibi, *J. Org. Chem.*, **37**, 2317 (1972).

(12) A similar problem has been encountered in attempted Diels–Alder cycloadditions to cycloocta-1,3-diene.[4a]

Previously,[1b] two alternative pathways have been suggested consistent with the formation of major amounts of anti-phenyl adducts **22** (n = 1) from cyclohexa-1,3-diene. According to Chart I the observed

CHART I

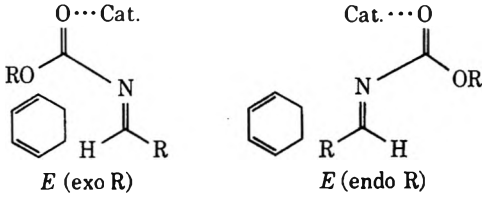


21 **22**

kinetically derived anti stereochemistry for the phenyl substituent in the formation of **1b** might result from electrophilic attack by iminourethane so that the bulkier phenyl substituent of the imine is oriented toward the less hindered face of the diene. By this argument the imine phenyl substituent will preferentially enter from the side syn to the diene, form a single carbon–carbon bond and allylic cation **21**, and finally collapse following bond rotation to form anti-phenyl product **22**.

For cycloheptatriene initial cationic attack by the complexed imine on the convex face of the triene terminus should be favored with the phenyl group away from the methylene bridge and syn to the olefinic bonds. In order to collapse to product, an initially formed cationic species must undergo a conformational inversion, the result of which locates the rotor substituent in a suitable position for bonding to form the anti-phenyl product **11** of [6 + 2] cycloaddition. Chart II does not explain the failure to observe a

CHART II

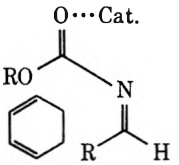


E (exo R) *E* (endo R)

preference for the syn-phenyl isomer **7** for reactions of cyclohepta-1,3-diene. Examination of Scheme I might however, provide an answer to this problem. Although initial electrophilic attack may occur with the bulkier substituent oriented over the diene portion of the ring, the initially formed allylic cation **17** can behave in a number of ways. The cation can undergo a rotation and ring closure to form bicyclic amine **18**, it can undergo a conformational inversion whereby the urethane is no longer in a suitable position for intramolecular ring closure and then lose a proton to form a substituted diene **19**, or it can be attacked by external nucleophile to form higher molecular weight material **20**. The final stereochemical course of the cycloaddition would then be the resultant of numerous competing intra- and intermolecular processes. Molecular models indicate that rotation of the substitutent on the allylic cation **17** formed from cyclohepta-1,3-diene is somewhat restricted by the trimethylene bridge. Also, the overall yield of bicyclic adducts **4** (13%) and **6** + **7** (11%), compared to the yields of bicyclic adducts **1** from cyclohexa-1,3-diene (40–50%), indicates the importance of alternative reaction modes for the cation from cyclohepta-1,3-diene.

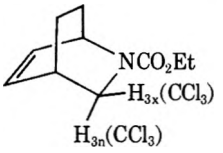
According to Chart II, a cyclic process might involve cycloaddition of an acid-complexed (*E*)-iminourethane by initial formation of a carbon–carbon bond followed by ring closure. The observed reaction stereochemistry will reflect the relative substituent preferences for the syn position between the substituent on nitrogen and those on carbon of the imine. In the present instance the competition would favor a syn orientation for an acid-complexed urethane functionality which might be attracted to the electron-rich diene. Since steric interaction between the bridge atoms and an anti substituent should vary with the diene employed, variations in reaction stereochemistry may reflect different substituent preferences in the system under investigation. Chart III, involving cycloaddition of (*Z*)-iminourethanes, is less likely, since the bulkier imine substituents should prefer the sterically less hindered side of the diene leading to a syn adduct preference, which was not observed. For the boron trifluoride catalyzed cycloaddition of the imine from 5-methoxy-3-phenylhydantoin[13] with cyclohexa-1,3-diene, stereospecific formation of syn adduct was observed in agreement with this argument.

CHART III



Z (endo R)

Synthesis of *N*-carbethoxytrichloromethylimine[14] and reaction with cyclohexa-1,3-diene afforded 3-trichloromethyl-*N*-carbethoxy-5,6-dehydrosioquinuclidine (**21**), which contained 80% of the *syn*-trichloromethyl



21a, exo CCl_3
b, endo CCl_3

isomer.[15] The formation of syn product is best explained by Chart II, in which steric interaction of the bulky trichloromethyl group with the methylene bridge of the diene results in a preference for the less hindered syn orientation. Chart I, on the other hand, should

(13) (a) D. Ben-Ishai and E. Goldstein, *Tetrahedron*, **27**, 3119 (1971). (b) E. Goldstein and D. Ben-Ishai, *Tetrahedron Lett.*, 2631 (1969). (c) We have obtained a single stereoisomer in which the C-3 proton does not exhibit long-range W-plan coupling. This proton is likely anti and the C-3 substituent is thus syn oriented.

(14) H. Ulrich, B. Tucker, and A. Sayigh, *J. Org. Chem.*, **33**, 2887 (1968).

(15) Thermal and acid-catalyzed reactions of halomethylimines with dienes are to be reported elsewhere. Isomer ratios **21a**:**21b** were determined from the nmr resonances (benzene-d_6) for H_{3x} (δ 4.76, d, J = 3 Hz) and H_{3n} (δ 4.42, q, J = 3, 1.3 Hz).

have led to a preference for the *anti*-trichloromethyl isomer.

In conclusion, the stereochemical course of the present cycloadditions is likely explained as proceeding *via* a stepwise cyclic transition state involving (*E*)-iminourethanes. However, predictions of product structures and stereochemistries based on such a model must be tempered by the recognition that allylic cations may play an important role.

Experimental Section

The nmr spectra were determined on a Varian Associates XL-100-15 spectrometer using tetramethylsilane (TMS) as an internal standard. Solutions of 5–10% solute in CCl_4, $CDCl_3$, or acetone-d_6, all containing 1% TMS, were used for nmr measurements. Couplings and coupling constants were where necessary obtained with the aid of decoupling experiments. All vpc work was performed using a 15 ft × 0.25 in., 2% XF-1150 on Chromosorb W column. Stereoisomer ratios obtained by nmr analysis of prepped crude reaction mixtures or distilled material were in agreement.

General Procedure for the Reaction of Alkylideneurethanes with Dienes.—A solution of the diene (0.125 mol) in 100 ml of dry benzene was added dropwise over 30 min to a stirred refluxing solution of alkylidenebisurethane (0.125 mol) and 5 g of boron trifluoride etherate in 200 ml of dry benzene. After 8–24 hr reflux the reaction solution was cooled, washed with water, aqueous sodium carbonate, dilute HCl, and water, and dried over magnesium sulfate. After removal of solvent the oil was diluted 10:1 with boiling *n*-heptane, which was then decanted from insolubles. The solvent was then removed *in vacuo* and the product was isolated by distillation and vpc.

***N*-Carbethoxy-6-azabicyclo[3.2.2]non-8-ene (4).**—Cyclohepta-1,3-diene (1.8 g, 0.02 mol) in 15 ml of benzene was added dropwise to a refluxing solution of methylenebisurethane (3.7 g, 0.02 mol) and boron trifluoride etherate (0.5 ml) in 100 ml of dry benzene. Work-up after 18 hr reflux as above afforded 1.45 g of an oil which was distilled (70–72°, 0.01 mm). The bicyclic product (400 mg, 13%) was purified by vpc (145°, retention time 11 min) to separate it from a small quantity of diene 5 (21 min) identified by comparison of its spectral parameters with those reported by Hobson.[2] The bicyclic adduct had spectral parameters ir (film) 1675 cm^{-1}, nmr (acetone-d_6) δ 1.58 (b, $H_{2,3,4}$), 2.60 (b, H_1), 4.10 (OCH_2), 1.20 (CH_3); see Table I.

7-Phenyl-6-azabicyclo[3.2.2]non-8-enes (6 and 7).—Boron trifluoride etherate (0.5 ml) and benzalbisurethane (13.3 g, 0.05 mol) in dry benzene (250 ml) were heated to reflux and cyclohepta-1,3-diene (4.7 g, 0.05 mol) was added dropwise over 30 min. After 8 hr reflux the reaction mixture was worked up to yield 7.4 g of crude oil which upon distillation (160°, 0.01 mm) afforded 1.5 g (11%) of 6 and 7: vpc (200°) retention time 10 min; ir (film) 1675 cm^{-1}; nmr ($CDCl_3$) for syn-phenyl 6, δ 2.65 (H_1), 1.68 and 1.28 ($H_{2,3,4}$), 5.00 (H_5), 7.18 (Ph), 3.90 (OCH_2), 0.84 (CH_3), and see Table I; nmr for anti-phenyl 7 δ 2.65 (H_1), 1.68 and 1.28 ($H_{2,3,4}$), 4.92 (H_5), 7.18 (Ph), 2.90 (OCH_2), 0.84 (CH_3), and see Table I. The ratio of anti (6) to syn (7) isomers as determined by comparison of integrated areas of H_{7x} for the syn-phenyl isomer and H_8 of the anti-phenyl isomer was 50:50.

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.02; H, 7.75; N, 5.28.

***N*-Carbethoxy-7-azabicyclo[4.2.1]nona-2,4-diene (10).**—Boron trifluoride etherate (5.0 g, 0.035 mol) and methylenebisurethane (24.0 g, 0.126 mol) in dry benzene (250 ml) were refluxed and cyclohepta-1,3,5-triene (11.6 g, 0.125 mol) was added dropwise over 30 min. After 8 hr reflux and work-up, distillation afforded 5.5 g (23% yield) of colorless oil 10: bp 84–87° (0.2 mm); vpc (150°) retention time 9 min; ir (CCl_4) 1690 cm^{-1}; uv (CH_3CN) λ_{max} 264 mμ (ϵ 3760), 240 (3320); nmr, see Table II. Only viscous tar remained in the distillation pot.

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.21; H, 7.85; N, 7.42.

8-Phenyl-*N*-carbethoxy-7-azabicyclo[4.2.1]nona-2,4-diene (11 and 12).—Boron trifluoride etherate (2.5 g, 0.018 mol) and benzalbisurethane (16.8 g, 0.063 mol) were refluxed in dry benzene (200 ml), and 1,3,5-cycloheptatriene (5.8 g, 0.063 mol) was added dropwise over 30 min. After 8 hr reflux, work-up and distillation of the residue afforded a forerun of benzylurethane 14 (1.8 g, 16% yield), bp 115–120° (0.15 mm), nmr ($CDCl_3$) δ 7.14, 5.64 (b), 4.2 (d, J = 6 Hz), 4.00 (q, J = 7 Hz), 1.10 (t, J = 7 Hz), identical with an authentic sample prepared from benzylamine and ethyl chloroformate. The product (1.6 g, 10% yield) was obtained as a viscous oil, bp 130–135° (0.15 mm), ir (CCl_4) 1695 cm^{-1}, uv (EtOH) λ_{max} 264 mμ (ϵ 3900), nmr, see Table II. The percentage of syn isomer 12 was determined by comparison of the integrated area for H_1 of 12 with H_6 for both isomers.

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.65; H, 7.27; N, 5.49.

Reaction of Methylenebisurethane with Cycloocta-1,3-diene (15).—Boron trifluoride etherate (0.5 ml) and methylenebisurethane (9.4 g, 0.05 mol) were refluxed in dry benzene (300 ml) containing cupric bromide, and cycloocta-1,3-diene (5.4 g, 0.05 mol) was added dropwise over 30 min. After overnight reflux, work-up afforded a crude oil which upon distillation (130–135°, 0.2 mm) afforded 2.0 g (27%) of diene 18: vpc (165°) retention time 15 min; ir (film) 1670, 3220 cm^{-1}; uv (EtOH) λ_{max} 227 mμ (ϵ 9000); nmr ($CDCl_3$) δ 5.6–5.5 (complex olefinic), 5.22 (NH), 4.08 (OCH_2), 3.75 (CH_2N, J = 6 Hz), 2.12 (allylic), 1.50 (methylene), 1.20 (CH_3).

Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.90; H, 9.09; N, 6.70. Found: C, 68.78; H, 9.15; N, 6.71.

Attempted Reaction of Methylenebisurethane with Cyclopentadiene.—Reaction of cyclopentadiene and methylenebisurethane as described according to the general procedure did not afford 1:1 diene–methylenebisurethane adducts upon work-up. Only higher molecular weight materials resulted.

Acknowledgment.—This research was supported by grants from the National Institutes of Health (CA 12020), the Research Corporation, and an American Cancer Society Institutional Grant.

Registry No.—**2**, 3693-53-6; **3**, 3693-54-7; **4**, 40792-14-5, 40792-15-2; **6**, 40792-16-3; **7**, 40792-17-4; **10**, 40792-18-5; **11**, 40792-19-6; **12**, 40792-20-9; **14**, 2621-78-5; **15**, 40792-21-0; cyclohepta-1,3-diene, 4054-38-0; cyclohepta-1,3,5-triene, 544-25-2.

Stereochemistry and Mechanism of the Ritter Reaction of Bromohydrins to Give 1-Amido-2-bromoalkanes and Ring Closure to Give 2-Oxazolines

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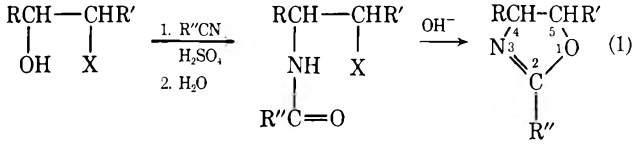
Received March 1, 1973

The stereochemistry of the Ritter reaction of bromohydrins has been investigated. It is shown that the reaction proceeds with complete retention, *e.g.*, *threo*-3-bromo-2-butanol (**1**) with acetonitrile or benzonitrile in the presence of sulfuric acid gave exclusively *threo*-2-acetamido-3-bromobutane (**3a**) and *threo*-2-benzamido-3-bromobutane (**3b**), respectively. Similarly, *erythro*-3-bromo-2-butanol (**2**) with acetonitrile and benzonitrile gave exclusively *erythro*-2-acetamido-3-bromobutane (**4a**) and *erythro*-2-benzamido-3-bromobutane (**4b**), respectively. The observed complete retention is explained by a mechanism over bridged bromonium ions. The bromoamides are not stable but ring close spontaneously to give the hydrobromide salts of the corresponding 2-oxazolines. The nmr spectra of the latter salts are discussed.

Ritter and Lusskin have reported the preparation of 1-amido-2-haloalkanes by the reaction of a halohydrin with a nitrile in the presence of concentrated sulfuric acid.[1,2] The resulting 1-amido-2-haloalkanes can with base be ring closed to give the corresponding 2-oxazolines (eq 1).[1,3] Owing to our interest in 2-oxazolines[4] we

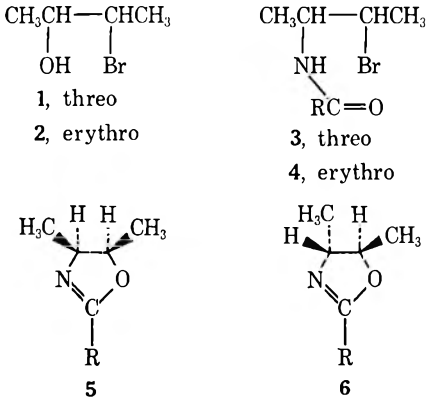


(1)

have investigated the stereochemistry of this reaction sequence.

Results

Using *threo*-3-bromo-2-butanol (**1**) as starting bromohydrin, reaction with acetonitrile and benzonitrile gave exclusively *threo*-2-acetamido-3-bromobutane (**3a**) and *threo*-2-benzamido-3-bromobutane (**3b**), respectively.



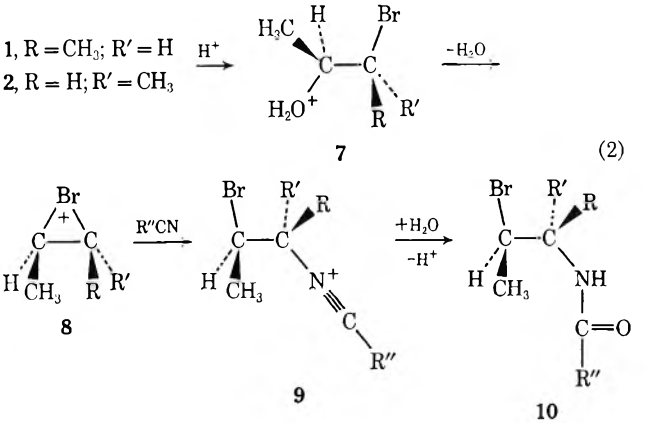
The stereochemistry of the bromoamides **3a** and **3b** was best demonstrated by their reaction with base to give exclusively *cis*-2,4,5-trimethyl-2-oxazoline (**5a**) and *cis*-4,5-dimethyl-2-phenyl-2-oxazoline (**5b**), respectively, in greater than 99% stereoisomeric purity as judged by gas-chromatographic analysis and comparison with the known compounds.[4] Since it is generally accepted that the ring-closure step forming the 2-oxazoline proceeds with Walden inversion,[5] the Ritter reaction step thus proceeds with complete retention.

erythro-3-Bromo-2-butanol (**2**) similarly with acetonitrile or benzonitrile in the presence of sulfuric acid led to practically pure *erythro*-2-acetamido-3-bromobutane (**4a**) and *erythro*-2-benzamido-3-bromobutane (**4b**), respectively, which on ring closure with base gave the corresponding *trans*-2-oxazolines, **6a** and **6b**.

The bromoamides **3** and **4** are not stable at room temperature. In solution they spontaneously ring close within a few hours to give the hydrobromide salts of the corresponding 2-oxazolines. This conversion can conveniently be followed by nmr spectroscopy. In the solid state the conversion to the oxazoline salt is slower. The instability of 1-amido-2-halides with respect to ring closure to 2-oxazolines has been noted before.[1,5]

Discussion

The Ritter reaction step, as inferred from the observed complete retention, most likely proceeds over a bridged bromonium ion according to the following mechanism (eq 2). The nature of the intermediates



(2)

and products **8**–**10** are, as it turns out, identical with those encountered by Hassner, *et al.*, in the addition of bromine and nitriles to olefins in the presence of silver salts.[6]

(1) R. M. Lusskin and J. J. Ritter, *J. Amer. Chem. Soc.*, **72**, 5577 (1950).

(2) The reaction of carbenium centers with nitriles is known as the Ritter reaction. Original publications: J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045, 4048 (1948).

(3) For a recent review of oxazoline chemistry see J. A. Frump, *Chem. Rev.*, **71**, 483 (1971).

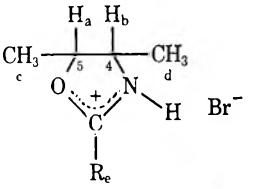
(4) R. A. Wohl and J. Cannie, *J. Org. Chem.*, **38**, 1787 (1973).

(5) See also H. W. Heine, *J. Amer. Chem. Soc.*, **78**, 3708 (1956); **79**, 907 (1957); and ref 6.

(6) A. Hassner, L. A. Levy, and R. Gault, *Tetrahedron Lett.*, **No. 27**, 3119 (1966).

TABLE I

NMR SPECTRA OF 2-OXAZOLINE HYDROBROMIDES



2-Oxazoline hydrobromide	Chemical shifts, δ (CDCl₃)[a]				
	H_a (at C-5)	H_b (at C-4)	H_c (at C-5)	H_d (at C-4)	H_e
cis-2,4,5-Trimethyl- (**5a**)	5.64 (oct)	4.83 (pent)[b]	1.57 (d)	1.47 (d)	2.61 (s)
	[4.52 (m)]	[3.95 (m)]	[1.16 (d)]	[1.03 (d)]	[1.81 (d)]
	J_{ab} = 9.8	J_{ba} = 9.8	J_{ca} = 6.5	J_{db} = 6.4	(R = CH_3)
cis-4,5-Dimethyl-2-phenyl- (**5b**)	5.70 (oct)	4.98 (pent)[b]	1.61 (d)	1.56 (d)	7.34–7.97 (m) + 8.41 (m)
	[4.66 (oct)]	[4.14 (oct)]	[1.25 (d)]	[1.14 (d)]	[7.25 (m) + 7.83 (m)]
	J_{ab} = 9.5	J_{ba} = 9.5	J_{ca} = 6.4	J_{db} = 6.3	(R = CH_3)
trans-2,4,5-Trimethyl- (**6a**)	5.03 (pent)[b]	4.31 (pent)[b]	1.70 (d)	1.59 (d)	2.65 (s)
	[3.95 (pent)]	[3.43 (m)]	[1.27 (d)]	[1.15 (d)]	[1.83 (d)]
	$J_{ab} \cong$ 6.9	J_{ba} = 6.9	K_{ca} = 7.9	J_{db} = 7.8	(R = C_6H_5]
trans-4,5-Dimethyl-2-phenyl- (**6b**)	5.07 (pent)[c]	4.40 (pent)[c]	1.71 (d)	1.71 (d)	7.33–8.04 (m) + 8.47 (m)
	[4.07 (pent)]	[3.64 (pent)]	[1.35 (d)]	[1.21 (d)]	[7.55 (m) + 7.83 (m)]
	J_{ab} = 7.9	J_{ba} = 7.9	J_{ca} = 6.4	J_{db} = 6.4	(R = C_6H_5)

[a] With respect to tetramethylsilane as internal standard. Chemical shifts in brackets are the values for the free 2-oxazoline bases in CCl_4 from ref 4. *J* values are observed splitting values in hertz. [b] Major splitting pattern in actually higher multiplet. [c] Predominating splitting pattern. Actually two overlapping quartets.

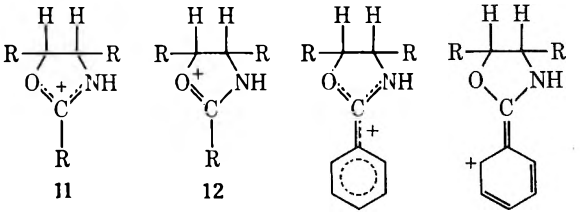
The 2,3-butylenebromonium ions **8** have also been discussed in the reaction of the bromohydrins **1** and **2** with HBr to give the corresponding 2,3-dibromobutanes,[7] in the reaction of 2-acetoxy-3-bromobutanes and 2,3-dibromobutanes with silver acetate in acetic acid,[8] and in the addition of bromine azide to *cis*- and *trans*-2-butene.[9] Recently they have been observed by Olah, *et al.*, by means of nmr spectroscopy in antimony pentafluoride–sulfur dioxide solution at low temperature.[10]

2-Oxazolines are of possible synthetic utility because they can be readily hydrolyzed to the corresponding amino alcohols. In the case of cyclic bromohydrins the resulting amino alcohols will possess the otherwise not readily available cis configuration.[6]

Nmr Spectra.—The nmr data of the hydrobromide salts of the 2-oxazolines are summarized in Table I. The general appearance of the spectra is very similar to that of the free 2-oxazoline bases.[4] The cis salts **5a** and **5b** have a vinical coupling constant J_{ab} of about 9.7 cps, and the trans compounds **6a** and **6b** have a coupling constant of 7–8 cps. Thus, as usual in more or less planar rings, cis-proton coupling is larger than trans-proton coupling.[4,11–13] The magnitude of the vicinal coupling contant J_{ab} is 1–2 Hz larger as compared to the values in the free oxazoline bases.[4]

The 4 and 5 methyl groups absorb at approximately 0.1 ppm higher field in the cis salts than in the corresponding trans isomers, whereas the 4 and 5 methine protons absorb at approximately 0.5 ppm lower field in the cis salts than in the trans compounds as is found in many cis–trans isomer pairs of planar three- to five-membered ring compounds.[4,14]

All protons appear in the hydrobromide salts as expected at lower field as compared with the same protons in the corresponding free 2-oxazolines. It is very interesting to note, however, that this downfield shift is very similar in magnitude for both the 4 and 5 substituents in spite of the fact that the 4 carbon atom is neighboring the protonated nitrogen atom. Actually the 5-methine proton which is neighboring the oxygen atom suffers a larger shift downfield than the 4-methine proton. In order to account for these data the resonance hybrid **11** may be invoked with the canonical



11 **12** **13** **14**

form **12** as an important contributor, *i.e.*, the positive charge is delocalized over both heteroatoms. The above assignment and conclusions agree with those by Pittman and coworkers, which are based on a large number of oxazolinium cations observed in sulfuric acid solution.[15]

In the case of the 2-phenyloxazolines **5b** and **6b** the positive charge is further delocalized into the aromatic ring according to the resonance hybrid **13**. The canonical form **14** and the canonical form with the positive charge in the other ortho position explain the observation that the two ortho hydrogen atoms of the phenyl group show the by far the largest shift downfield (*ca.* 0.6 ppm) of the aromatic protons as compared to their chemical shifts in the free bases.

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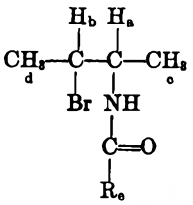
TABLE II

NMR SPECTRA OF 2-AMIDO-3-BROMOBUTANES



2-Amido-3-bromobutane	Chemical shifts, δ (CDCl₃)[a]				
	H_a	H_b	H_c	H_d	H_e
3a (threo)	← 4.25 (m) →		1.67 (d) J_{ca} = 6.8	1.25 (d) J_{db} = 6.4	2.06 (s) (R = CH_3)
3b (threo)	← 4.35 (m) →		1.73 (d) J_{ca} = 7.0	1.34 (d) J_{db} = 6.6	6.49 + 7.82 (m) (R = C_6H_5)
4a (erythro)	4.40 (oct) J_{ab} = 3.2	4.03 (m) J_{ba} = 3.2	1.67 (d) J_{ca} = 6.9	1.19 (d) J_{db} = 6.4	2.01 (s) (R = CH_3)
4b (erythro)	4.49 (oct) J_{ab} = 3.0	4.12 (m) J_{ba} = 3.0	1.17 (d) J_{ca} = 6.5	1.29 (d) J_{db} = 6.2	7.47 + 7.82 (m) (R = C_6H_5)

[a] With respect to tetramethylsilane as internal standard. *J* values are observed splitting values in hertz.

The 2-methyl group in the salts **5a** and **6a** appears essentially as a singlet, whereas in the free 2-oxazolines it couples with the 4-methine proton with a long-range coupling constant of approximately 1.5 cps.[4,16] The long-range coupling is, if present at all, much smaller in the salts as expected owing to the decreased double bond character of the C=N bond.[17]

The spectrum of a hydrobromide salt could be converted gradually into the spectrum of the free 2-oxazoline base by adding slightly moist potassium carbonate in small portions to the nmr tube.

Experimental Section

General Procedures.—Infrared spectra were taken on a Perkin-Elmer Model 137 sodium chloride spectrophotometer. Methylene chloride was used as a solvent. Nmr spectra were taken on a Varian T-60 nuclear magnetic resonance spectrometer. Gas chromatography was done on a Varian Model 90P gas chromatograph. Acetonitrile was distilled over phosphorous pentoxide. Benzonitrile was dried over molecular sieves 3A.

2-Amido-3-bromobutanes.—The method of Lusskin and Ritter was essentially followed.[1] To 0.3 mol of the nitrile, which was cooled in ice and stirred magnetically, 70 g of concentrated sulfuric acid was added slowly. After stirring for another 0.5 hr, 0.1 mol of the bromohydrin was slowly added in about 30 min. The solution was allowed to warm up to room temperature, kept for 3 hr at 35°, and then poured into 300 g of ice and water; 20 g of sodium carbonate was added in portions; and the solution was stirred for another 5–10 min. The individual halo amides were then isolated as described below.

The nmr spectra of all halo amides are summarized in Table II.

On prolonged standing of the solid or a solution all 2-amido-3-bromobutanes converted to the hydrobromide salts of the corresponding 2-oxazolines.

threo-**2-Acetamido-3-bromobutane** (**3a**)—The following work-up was done as rapidly as possible and with the temperature not exceeding room temperature. The aqueous reaction mixture, in which no precipitate had formed, was extracted three times with ether. After drying with magnesium sulfate, evaporation yielded 15.7 g (81%) of a colorless oil, which eventually solidified to an extremely hygroscopic solid.

threo-**2-Benzamido-3-bromobutane** (**3b**).—The precipitate formed in the aqueous reaction mixture was isolated by filtration and washed with 10% sodium carbonate solution, water, and pentane; 50 g of white crystals were obtained containing substantial amounts of benzamide. The material was not purified further for conversion to the 2-oxazoline **5b**.

erythro-**2-Acetamido-3-bromobutane** (**4a**).—The following work-up was done as rapidly as possible and with the temperature not exceeding room temperature. The aqueous reaction mixture, in which no precipitate had formed, was extracted three times with ether. After drying with magnesium sulfate, evaporation of the ether yielded 14.2 g (73%) of a colorless oil which solidified to an extremely hygroscopic solid.

erythro-**2-Benzamido-3-bromobutane** (**4b**).—The precipitate formed in the aqueous reaction mixture was isolated by filtration and washed successively with 10% sodium carbonate solution, water, and pentane; 44 g of white crystals were obtained which contained substantial amounts of benzamide. The material was not further purified for conversion to the 2-oxazoline **6b**. A much purer sample was obtained by rapidly treating the crude material with boiling water in order to extract the benzamide. This sample, which contained practically no benzamide, melted at 132–135°.

General Procedure for 2-Oxazolines.—A 50-mmol portion of the crude 2-amido-3-bromobutane was treated with 40 ml of 2 *N* sodium hydroxide solution and then steam distilled. The 4,5-dimethyl-2-phenyl-2-oxazolines **5b** and **6b** were isolated by extracting three times with ether, drying the combined ether phases with magnesium sulfate, and evaporating the ether. The 2,4,5-trimethyl-2-oxazolines **5a** and **6a** were isolated by extracting the steam distillate with ether in a Kutscher–Steudel apparatus, then drying the ether with magnesium sulfate and evaporating the ether through a short Vigreux column. Table III shows the yields. The gas chromatographic separations were performed on a 6-ft column of 15% Carbowax 20M on Gas-Chrom P with a flow rate of 90 ml/min. Column temperature was 104° for the *trans*- and *cis*-2,4,5-trimethyl-2-oxazolines **6a** and **5a**, which had retention times of 2.5 and 3 min, respectively. Column temperature was 215° for the *trans*- and *cis*-2-phenyl-2-oxazolines **6b** and **5b**, which had retention times of 2.7 and 3.7 min, respectively. The stereoisomeric purity of all 2-oxazolines exceeded 99%.

TABLE III

YIELDS OF 2-OXAZOLINES

2-Oxazoline	Yield, %[a]
cis-2,4,5-Trimethyl-2-oxazoline (**5a**)	33
trans-2,4,5-Trimethyl-2-oxazoline (**6a**)	31
cis-4,5-Dimethyl-2-phenyl-2-oxazoline (**5b**)	94
trans-4,5-Dimethyl-2-phenyl-2-oxazoline (**6b**)	87

[a] Crude weight yield based on initial bromohydrin. The isolated oxazolines are essentially pure as judged by their ir and nmr spectra and gas chromatograms.

Acknowledgment.—We wish to thank the Rutgers Research Council for financial support.

Registry No.—**1**, 19773-41-2; **2**, 19773 40-1; **3a**, 40891-89-2; **3b**, 40891-90-5; **4a**, 40891-91-6; **4b**, 40891-92-7; **5a**, 23236-41-1; **5b**, 36746-57-3; **6a**, 23336-75-6; **6b**, 38898-95-2.

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(17) See, however, the comments pertaining to footnote 361 in ref 15.

Reactions of an *N*-Hydroxyquinazoline Structurally Analogous to Oncogenic *N*-Hydroxypurines[1]

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Received April 5, 1973

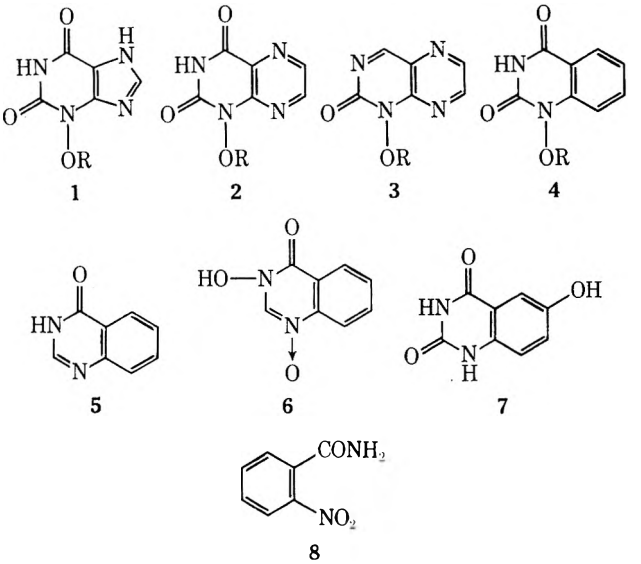
1,2,3,4-Tetrahydro-1-hydroxy-2,4-dioxoquinazoline, an analog of 3-hydroxyxanthine, was found to be less reactive than 3-hydroxyxanthine but more reactive than its pteridine analog. Thus, treatment of 1,2,3,4-tetrahydro-1-hydroxy-2,4-dioxoquinazoline with acetic anhydride gave a stable 1-acetoxy derivative. Upon treatment with phosphorus oxychloride it gave 6-chloro-1,2,3,4-tetrahydro-2,4-dioxoquinazoline, and with tosyl chloride, mesyl chloride, or *p*-nitrobenzenesulfonyl chloride it gave the corresponding 1,2,3,4-tetrahydro-2,4-dioxo-8-sulfonyloxyquinazolines. The formation of the 8-sulfonyloxyquinazolines probably proceeds *via* an intramolecular mechanism and the expected intermediate, 1,2,3,4-tetrahydro-2,4-dioxo-1-sulfonyloxyquinazoline, could be isolated. With peracetic acid 3,4-dihydro-4-oxoquinazoline gave 1,2,3,4-tetrahydro-1-hydroxy-2,4-dioxoquinazoline, rather than 1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxoquinazoline, as was reported by others.

Chemical[3-7] and biochemical[8,9] studies have shown that the oncogenicity[10,11] of 3-hydroxyxanthine and some of its derivatives is paralleled by unique chemical reactivities of esters of these *N*-hydroxypurines. In a reaction termed the 3-acyloxypurine 8-substitution reaction, 3-acetoxyxanthine (**1**, R = Ac) undergoes, under mild conditions, an SN1′ reaction with nucleophiles to yield 8-substituted xanthines.[3-6]

In an investigation of analogs of 3-hydroxyxanthine to determine the features required for this type of reactivity the initial study[12] was of the *N*-hydroxypteridines (**2** and **3**, R = Ac, Ms, or Ts), which failed to undergo any similar substitution reactions. Their lack of reactivity could be attributed to the π-deficient character of the pyrazine ring in pteridines, as opposed to the π-excessive character of the imidazole ring of purines.[13]

We now report the reactions of 1,2,3,4-tetrahydro-1-hydroxy-2,4-dioxoquinazoline (**4**, R = H). It is more analogous to 3-hydroxyxanthine (**1**, R = H) since the π-electron density of the benzene ring lies between those of the imidazole ring of **1** and the pyrazine ring of **2**. Therefore the tendency of **4** to undergo a substitution reaction is expected to be between those of **1** and **2**.

Chiang and Li claimed[14,15] that oxidation of 3,4-dihydro-4-oxoquinazoline (**5**) with peracetic acid gave 3,4-dihydro-3-hydroxy-4-oxoquinazoline 1-oxide (**6**) together with some 1,2,3,4-tetrahydro-6-hydroxy-2,4-dioxoquinazoline (**7**), *o*-nitrobenzamide (**8**), *N*-formyl-*o*-nitrobenzamide, and benzoic acid.[14] They also claimed that **7** was obtained from **6** by boiling with acetic acid, which would be comparable to the reaction we are studying. Reinvestigation of their work showed that the compound to which they assigned the structure **7** was actually **4** (R = H). Its nmr spectrum showed a 4-proton ABCD pattern in the aromatic region, and it was found to be identical with that of an authentic sample.



Authentic **4** (R = H) was prepared from 4-ethoxyquinazoline by an improvement of the published procedure.[16] When refluxed in acetic anhydride only the *N*-hydroxy function of **4** (R = H) was esterified, to yield **4** (R = Ac), and no products comparable to those from 3-hydroxyxanthine[3-6] resulted.

The 1-acetoxyquinazoline (**4**, R = Ac), unlike 3-acetoxyxanthine (**1**, R = Ac),[5] did not yield any substitution products when treated with a variety of nucleophiles, even under vigorous conditions. In boiling ethanol, only ethanolysis of **4** (R = Ac) to **4** (R = H) occurred, whereas the same treatment of **1** (R = Ac) gives 8-ethoxyxanthine in almost quantitative yield.[5]

When compound **4** (R = H) was refluxed with phosphorus oxychloride and phosphorus pentachloride, a substitution with elimination of the *N*-hydroxy group

(1) This investigation was supported in part by funds from the National Cancer Institute (Grant No. CA 08748). This is no. 51 in a series on Purine *N*-Oxides; no. 50 is ref 11.

(2) G. Salemnick is a David A. Gimbel Fellow.

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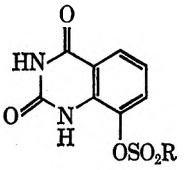
(15) W. L. F. Armarego in "Fused Pyrimidines, Part 1, Quinazoline," D. J. Brown, Ed., Wiley-Interscience, New York, N. Y., 1967, p 460.

(16) H. Yamanaka, *Chem. Pharm. Bull.*, **7**, 152 (1959).

TABLE I

NMR CHEMICAL SHIFTS (δ, PPM)[a] AND COUPLING CONSTANTS (Hz)

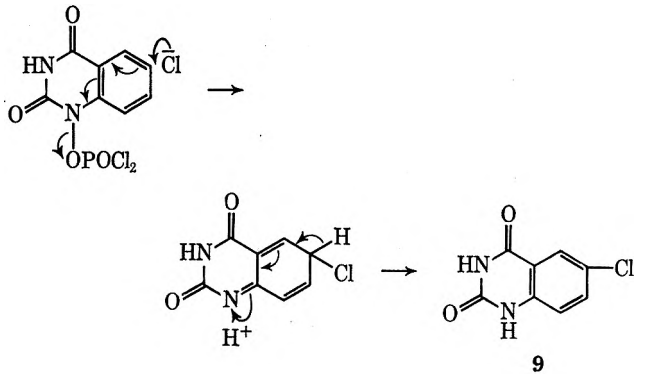


10

Compd	H⁶ (t)	H⁵ (dd)	H⁷ (dd)	N¹ (s), N³ (s)
10 (R = tolyl)[b]	7.17; $J_{6,5}$ = $J_{6,7}$ = 8	7.50; $J_{5,6}$ = 8, $J_{5,7}$ = 1.5	7.94; $J_{7,6}$ = 8, $J_{7,5}$ = 1.5	10.88;[c] 11.38[c]
10 (R = Me)[d]	7.23; $J_{6,5}$ = $J_{6,7}$ = 8	7.71; $J_{5,6}$ = 8, $J_{5,7}$ = 1.5	7.94; $J_{7,6}$ = 8, $J_{7,5}$ = 1.5	11.09;[c] 11.47[c]
10 (R = nitrophenyl)[e]	7.20; $J_{6,5}$ = $J_{6,7}$ = 8	7.56; $J_{5,6}$ = 8, $J_{5,7}$ = 1.5	7.90; $J_{7,6}$ = 8, $J_{7,5}$ = 1.5	10.98;[c] 11.38[c]

[a] Solvent DMSO-d_6. [b] Methyl singlet at 2.40, doublet at 7.44, H³′ + H⁵′, J = 8, doublet at 7.84, H²′ + H⁶′, J = 8.0. [c] Exchangeable with D_2O. [d] Methyl singlet at 3.61. [e] Doublet at 8.22, H²′ + H⁶′, J = 8.0; doublet at 8.47, H³′ + H⁵′, J = 8.0.

did occur, and 6-chloro-1,2,3,4-tetrahydro-1,4-dioxoquinazoline[17] was obtained. Presumably the dichlorophosphate ester was first formed, and this more effective leaving group facilitated the cleavage of the N–O bond. Nucleophilic substitution by chloride ion, an intermolecular process, gave **9**. Similar mechanisms

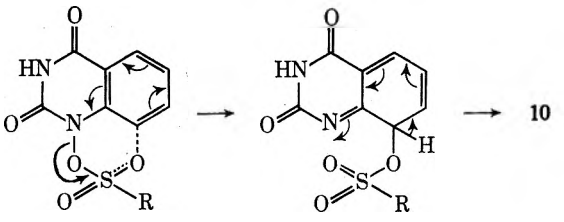


9

are involved in the reactions of pyridine *N*-oxide with phosphorus pentachloride[18,19] and 1,X-naphthyridine 1-oxides[20] with phosphorus oxychloride.

When 1,2,3,4-tetrahydro-1-hydroxy-2,4-dioxoquinazoline (**4**, R = H) was treated with tosyl chloride, mesyl chloride, or *p*-nitrobenzenesulfonyl chloride in pyridine at room temperature, the products were probably the result of an intramolecular rearrangement. The respective 8-sulfonyloxyquinazolines (**10**, R = Me, *p*-tolyl, *p*-$NO_2C_6H_4$) were obtained. The position of substitution was indicated by nmr spectra (Table I) which were quite definitive and which showed that compounds **10** (R = Me, *p*-tolyl, *p*-$NO_2C_6H_4$) each bore a substituent at the 8 position (see Table I). In addition, the position of the substitution was confirmed by treatment of compounds **10** (R = Me) or **10** (R = *p*-tolyl) with 0.1 *N* sodium hydroxide to give 1,2,3,4-tetrahydro-8-hydroxy-2,4-dioxoquinazoline, which was prepared unambiguously from 3-hydroxyanthranilic acid. Boiling **4** (R = H) with tosyl chloride in ethanol gave 1-ethoxy-1,2,3,4-tetrahydro-2,4-dioxoquinoline (**4**, R = Et) rather than a sulfonyloxy derivative. Similar treatment with even a large excess of tosyl chloride in methanol did not yield the 1-methoxy compound. The structure of the ethoxy compound was established by its nmr spectrum which gave an ABCD pattern in the aromatic region, and one OEt and one NH signal.

An attempted Reissert reaction of **4** (R = H) with benzoyl chloride in the presence of potassium cyanide in DMF at temperatures up to 100° gave unchanged starting material. With tosyl chloride, to obtain a better leaving group, and potassium cyanide (2 equiv) both 1,2,3,4-tetrahydro-2,4-dioxo-1-tosyloxyquinazoline (**4** = SO_2-*p*-tolyl) and the 8-tosyloxy isomer were obtained. With less potassium cyanide the formation of the 1-tosyloxyquinazoline was reduced. When sodium cyanide was used instead of potassium cyanide, the only product was the 8-tosyloxyquinazoline. The structure of the 1-tosyl isomer was confirmed from its nmr spectrum which showed a methyl signal at δ 2.40, aromatic protons, a multiplet at δ 7–8 integrating for eight protons, and a single exchangeable NH at δ 11.33. Since the reaction of **4** (R = H) with tosyl chloride gave only **10**, even under the influence of stronger competitive nucleophiles such as pyridine or cyanide ion, the formation of the 8-sulfonyloxyquinazoline is most likely the result of an intramolecular reaction within a solvent cage, as



A molecular model of the 1-tosyloxyquinazoline shows the oxygen of the $-SO_2$ group to be close to the 8 position of the quinazoline, and thus able to form a six-membered cyclic transition state. Cleavage of the N–O bond, hydrogen migration, and rearomatization would then yield the 8-sulfonyloxyquinazoline. An intramolecular mechanism is supported by the finding of only the 8-sulfonyloxyquinazolines, and no 6-substitution products. This rearrangement is comparable to that of 1-hydroxycarbostyril to 8-tosyloxy-

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2-quinolone,[21] which has been proved by radioisotope labeling to be partially intramolecular. This rearrangement contrasts with the intermolecular S_N1' reaction in $POCl_3$–PCl_5, which yields **9**.

Esters of the 1-hydroxyquinazoline analog are thus intermediate in reactivity between the 1-hydroxypteridine analog[12] and 3-acetoxyxanthine.[5,6] They do undergo reactions involving substitution with rearrangement, but only with leaving groups better than acetate. This is in agreement with predictions made from the relative π characters of the benzene, pyrazine, and imidazole rings in the fused ring systems. Should an ester of 1,2,3,4-tetrahydro-1-hydroxy-2,4-dioxoquinazoline be formed *in vivo*,[9] it would not be expected to be reactive under physiological conditions, and it is improbable that **4** (R = H) would be an oncogen.[11]

Experimental Section

The uv spectra were determined with a Cary 15 spectrometer. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Nmr spectra were determined with a Varian A-60 spectrometer, in Me_2SO-d_6 with tetramethylsilane as an internal reference. The melting points are uncorrected. Paper chromatography, ascending, on Whatman No. 1 paper was used to check the purity of each of the compounds prepared. For Dowex 50 chromatography BioRad AG-50, 8X, 200–400 mesh [H^+] resin was used.

4-Ethoxy-1,2-dihydro-1-hydroxy-2-oxoquinazoline (12) and 1,2,3,4-Tetrahydro-1-hydroxy-2,4-dioxoquinazoline (4, R = H).—**12** was prepared from 4-ethoxyquinazoline[16] by oxidation with 2 equiv, instead of 1 equiv, of ethereal perphthalic acid. Upon isolation as described an improved yield of **12** (51%, lit.[16] 26%) and some 4-ethoxyquinazoline 1-oxide (17%) was obtained. Hydrolysis of **12** in 50% acetic acid gave a quantitative yield of **4** (R = H): uv max in methanol, nm ($\epsilon \times 10^{-3}$), 246 (8.48), 316 (3.64); nmr δ 7.62 (m, 4 H, $H^5 + H^6 + H^7 + H^8$), 11.10 (s, 1 H, H^1), 11.60 (s, 1 H, H^3).

1-Acetoxy-1,2,3,4-tetrahydro-2,4-dioxoquinazoline (4, R = Ac).[22]—**4** (R = H) (0.60 g, 0.0033 mol) was refluxed with acetic anhydride (10 ml) for 4 hr and cooled. The **4** (R = Ac) was collected and recrystallized from ethanol, 0.40 g (55%), colorless needles: mp 225°; uv max in ethanol, nm ($\epsilon \times 10^{-3}$), 243 (8.42), 308 (3.96).

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.52; H, 3.66; N, 12.72. Found: C, 54.26; H, 3.63; N, 12.45.

6-Chloro-1,2,3,4-tetrahydro-2,4-dioxoquinaoline (9).—A stirred solution of **4** (R = H) (0.45 g, 0.0025 mol) and phosphorus pentachloride (1.6 g) in phosphorus oxychloride (5 ml) was refluxed for 1.5 hr. The cooled mixture was poured into ice–water (100 ml) and the clear supernatant was decanted. The solid residue was extracted with ether (100 ml); the ether was washed with water, dried over sodium sulfate, and evaporated to dryness. Concentrated HCl (20 ml) was added, the solution heated under reflux for 3 hr, and **9** crystallized on cooling. Recrystallization from 50% acetic acid gave **9**, 0.10 g (20%), colorless needles: mp 344° (lit.[17] mp 345–348°); nmr δ 7.20 (d, 1 H, H^8, $J_{8,7}$ = 8.5 Hz), 7.71 (dd, 1 H, H^7, $J_{7,8}$ = 8.5 Hz, $J_{7,5}$ = 2Hz), 7.84 (d, 1 H, H^5, $J_{5,7}$ = 2 Hz), 11.25, 11.41 (2, 1 H each, N_1H, N_3H, exchangeable with D_2O); uv max in ethanol, nm ($\epsilon \times 10^{-3}$), 245 (11.5), 252 (11.3), 322 (3.42).

Anal. Calcd for $C_8H_5ClN_2O_2$: C, 48.87; H, 2.56; N, 14.25; Cl, 18.03. Found: C, 48.62; H, 2.61; N, 13.99; Cl, 18.19.

1,2,3,4-Tetrahydro-2,4-dioxo-8-tosyloxyquinazoline (10, R = *p*-Tolyl). A.—To a stirred solution of **4** (R = H) (0.178 g, 0.001 mol) in dry pyridine (4 ml), tosyl chloride (0.210 g, 0.0011 mol) was added in small portions at room temperature. After stirring for 48 hr most of the pyridine was evaporated under vacuum (<40°), water was added, and the white precipitate was collected. Two recrystallizations from ethanol gave the **10** (R = *p*-tolyl), 0.13 g (39%), colorless crystals, mp 220°.

B.—Tosyl chloride (420 mg, 0.0022 mol) was added to a solution of the **4** (R = H) (356 mg, 0.002 mol) and sodium cyanide (212 mg, 0.004 mol) in dry DMF (45 ml). The reaction mixture was stirred at room temperature for 61 hr. The DMF was evaporated under vacuum (<40°), and a small amount of water was added to the oily residue to precipitate the tosyloxyquinazoline. Recrystallization of the crude product from methanol gave the pure 8-tosyloxyquinazoline, 158 mg (24%): uv max in ethanol, nm ($\epsilon \times 10^{-3}$), 307 (4.12).

Anal. Calcd for $C_{15}H_{12}N_2O_5S$: C, 54.21; H, 3.64; N, 8.43; S, 9.65. Found: C, 54.38; H, 3.61; N, 8.37; S, 9.83.

1,2,3,4-Tetrahydro-8-mesyloxy-2,4-dioxoquinazoline (10, R = Me).—Methanesulfonyl chloride (0.1 ml) was added to a cooled stirred solution of **4** (R = H) (0.178 g, 0.001 mol) in pyridine (4 ml). It was stirred for 72 hr at room temperature; the pyridine was evaporated under vacuum, water added, and the white precipitate collected. Two recrystallizations from 50% acetic acid gave the **10** (R = Me), 0.077 g (30%): mp 345° dec; uv max in ethanol, nm ($\epsilon \times 10^{-3}$), 312 (saturated solution).

Anal. Calcd for $C_9H_8N_2O_5S$: C, 42.18; H, 3.15; N, 10.93; S, 12.51. Found: C, 42.37; H, 3.26; N, 11.00; S, 12.31.

8-*p*-Nitrobenzenesulfonyloxy-1,2,3,4-tetrahydro-2,4-dioxoquinazoline (10, R = *p*-$NO_2C_6H_4$).—This was prepared in a manner similar to that for tosyloxyquinazoline and yielded light yellow crystals (44%): mp 282–283°; uv max in methanol, nm ($\epsilon \times 10^{-3}$), 243 (17.1), 310 (4.20).

Anal. Calcd for $C_{14}H_9N_3O_7S$: C, 46.28; H, 2.49; N, 11.56; S, 8.82. Found: C, 46.14; H, 2.36; N, 11.42; S, 8.91.

1,2,3,4-Tetrahydro-2,4-dioxo-1-tosyloxyquinazoline (4, R = SO_2-*p*-tolyl).—*p*-Toluenesulfonyl chloride (210 mg, 0.0011 mol) was added to a solution of **4** (R = H) (178 mg, 0.001 mol) and potassium cyanide (130 mg, 0.002 mol) in DMF (30 ml). After stirring at room temperature for 4 days, the DMF was evaporated nearly to dryness under vacuum (<40°). The addition of water to the oily residue precipitated **4** (R = SO_2-*p*-tolyl) (205 mg), and two recrystallizations from methanol gave 57 mg (19%) of colorless crystals: mp 260–261°; uv max in ethanol, nm ($\epsilon \times 10^{-3}$), 314 (3.65).

When 1 equiv of potassium cyanide was used, no 1-tosyloxy derivative could be isolated in pure form.

Anal. Calcd for $C_{15}H_{12}N_2O_5S$: C, 54.21; H, 3.64; N, 8.43; S, 9.65. Found: C, 54.09; H, 3.70; N, 8.53; S, 9.69.

1,2,3,4-Tetrahydro-8-hydroxy-2,4-dioxoquinazoline (11). A.—Potassium cyanate (0.360 g, 0.0045 mol) in water (5 ml) was added in portions to a suspension of 3-hydroxyanthranilic acid (0.530 g, 0.0034 mol) in water (15 ml) containing acetic acid (0.26 ml). After being stirred 25 min at 35° sodium hydroxide (4.78 g, 0.12 mol) was added in small portions, with cooling (<30°). After 2 days the solution was brought to pH 5 with 50% H_2SO_4 and the precipitate collected. It was absorbed on a Dowex 50 [H^+] column (4.5 × 26 cm) which was eluted with water. Evaporation of the solution gave **11**, 150 mg (23%), which was recrystallized from water as white needles: mp >300° (sublimation); ferric chloride test green in ethanol; paper chromatography CH_3CN:H_2O (3:1) R_f 0.80, CH_3CN:H_2O:NH_4OH (7:2:1) R_f 0.57, NH_4Cl (3%) R_f 0.39; uv max in methanol, nm ($\epsilon \times 10^{-3}$), 322 (3.57).

Anal. Calcd for $C_8H_6N_2O_3 \cdot {}^1/_2H_2O$: C, 51.34; H, 3.77; N, 14.96. Found: C, 51.56; H, 3.50; N, 14.90.

B.—The 8-tosyloxyquinazoline (0.166 g) was added to 0.5 *N* NaOH (20 ml) and heated on the steam bath for 6 hr. The mixture was absorbed on a Dowex 50 [H^+] column (4.5 × 26 cm), from which elution with water gave *p*-toluenesulfonic acid and then the product. The concentrated eluate (40 mg, 43%) of the product was recrystallized from water as white needles: mp >300° (sublimation); ferric chloride test green in ethanol; paper chromatography CH_3CN:H_2O (3:1) R_f 0.80, CH_3CN:H_2O:NH_4OH (7:3:1) R_f 0.57, NH_4Cl (3%) R_f 0.39.

Anal. Calcd for $C_8H_6N_2O_3 \cdot {}^1/_2H_2O$: C, 51.34; H, 3.77; N, 14.96. Found: C, 51.42; H, 3.64; N, 14.68.

1-Ethoxy-1,2,3,4-tetrahydro-2,4-dioxoquinazoline (4, R = Et).—**4** (R = H) (500 mg) in ethanol (50 ml) was refluxed with tosyl chloride (500 mg) for 3 hr and the solution evaporated to dryness. The residue in dilute sodium hydroxide (0.1 *N*, 20 ml) was absorbed on a Dowex 50 [H^+] column. Elution with water gave the unchanged starting material (330 mg) as the first fraction, followed by **4** (R = Et), 190 mg: mp 170° (from water); uv max in methanol, nm ($\epsilon \times 10^{-3}$), 244 (8.87), 312 (3.99).

(21) K. Ogino and S. Oae, *Tetrahedron*, **27**, 6037 (1971).

(22) This compound was incorrectly identified as 6-acetoxy-1,2,3,4-tetrahydro-2,4-dioxoquinazoline.[14]

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.05; H, 4.84; N, 13.39.

Acknowledgment.—We thank Mr. Marvin J. Olsen and Mr. Gerald Reiser for the nmr and uv spectra.

Registry No.—**4** (R = H), 13300-21-5; **4** (R = Ac), 40919-19-5; **4** (R = SO_2-*p*-tolyl), 40919-20-8; **4** (R = Et), 40919-21-9; **9**, 1640-60-4; **10** (R = *p*-tolyl), 40919-23-1; **10** (R = Me), 40919-24-2; **10** (R = *p*-nitrophenyl), 40919-25-3; **11**, 40919-26-4; **12**, 40919-27-5; phosphorus pentachloride, 10026-13-8; tosyl chloride, 98-59-9; 3-hydroxyanthranilic acid, 548-93-6.

Quinoxaline 1,4-Dioxides. Nucleophilic Displacement of Sulfinyl and Sulfonyl Groups in Acid Media. A Novel Method for the Preparation of 2-Haloquinoxaline 1,4-Dioxides

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The oxidation of the quinoxaline 1,4-dioxides **2a** and **2b** with *1* or *2* equiv of *m*-chloroperbenzoic acid furnished the corresponding sulfoxides (**3a** and **3b**) and sulfones (**4a** and **4b**), respectively, in high yields. Treatment of these compounds with aqueous halogen acids furnished the corresponding 2-haloquinoxaline 1,4-dioxides (**5**), almost in quantitative yields. The action of organic acids on these sulfoxides and sulfones produced, instead of the expected 2-acyloxy derivatives, esters of 1-hydroxyquinoxalin-2-one 4-oxide (**6**). The mechanism and the potential synthetic utility are discussed.

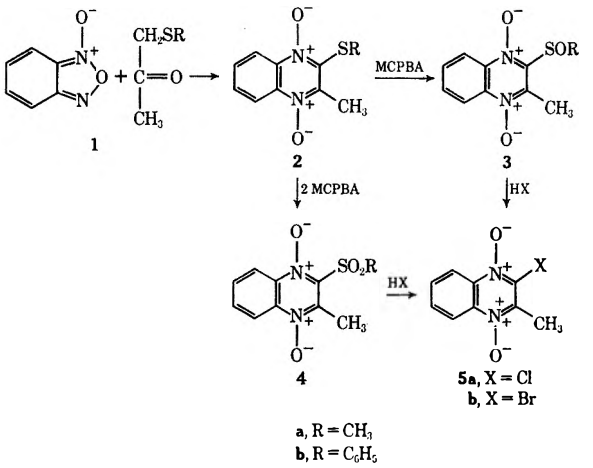
There are three general methods for the preparation of quinoxaline 1,4-dioxides: peracid oxidation of the parent amine,[2] the condensation of enamines and enolates with benzofurazan 1-oxide (BFO, **1**),[3] and the condensation of α diketones with *o*-benzoquinone dioxime.[4] However, none of these methods can be used for the synthesis of 2-haloquinoxaline 1,4-dioxides, owing to difficulties encountered in the oxidation of 2-halo aromatic amines, and the failure of 2-halo ketones to react successfully with BFO. The present work describes a novel nucleophilic displacement of sulfinyl and sulfonyl groups which provides a simple method for the synthesis of 2-haloquinoxaline 1,4-dioxides in high yield.

Preparation of the starting materials was accomplished according to earlier procedures.[3] Thus, condensation of BFO with acetonylmethyl sulfide and acetonylphenyl sulfide[5] furnished the corresponding quinoxaline 1,4-dioxides **2a** and **2b**, respectively (50–60%). These were in turn oxidized with either *1* or *2* equiv of *m*-chloroperbenzoic acid (MCPBA) to yield the corresponding sulfoxides (**3a** and **3b**) and sulfones (**4a** and **4b**), respectively, in 80–90% yields.

Treatment of **3** or **4** with aqueous hydrochloric or hydrobromic acid under mild conditions gave the quinoxaline 1,4-dioxides **5a** and **5b**, respectively, almost in quantitative yields. Scheme I summarizes the above reactions.

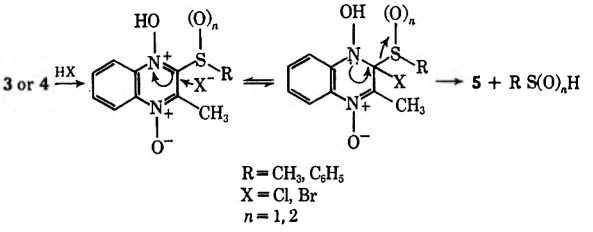
The structures of **5a** and **5b** were based on mass spectral data, which showed the expected molecular ion doublets indicating the presence of chlorine and bromine. The nmr spectra of **5a** and **5b** were consistent with the proposed structures and each consisted of a three-hydrogen methyl singlet at δ 2.76 (**5a**) and 2.88 (**5b**). The typical aromatic A_2B_2 pattern observed for other quinoxaline 1,4-dioxides was preserved in **5a** and **5b** and appeared at δ 7.78 and 8.6.

SCHEME I



A plausible mechanism for these reactions is depicted in Scheme II.

SCHEME II



Initial protonation of the *N*-oxide group is probably involved followed by halide attack at C-2, with subsequent elimination of a sulfinic or sulfenic acid. Support for this mechanism came from the reaction of hydrochloric acid with the phenyl sulfoxide **3b**. In addition to the chloro compound **5a**, there were isolated two additional compounds, namely diphenyl disulfide[6] and *S*-phenyl benzenethiosulfonate[7] in 84

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(2) E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York, N. Y., 1967, pp 31, 35, 44.

(3) (a) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 3253 (1965); (b) *J. Org. Chem.*, **31**, 4067 (1966).

(4) E. Abushanab, *J. Org. Chem.*, **35**, 4279 (1970).

(5) C. K. Bradsher, R. C. Brown, and R. J. Grantham, *J. Amer. Chem. Soc.*, **76**, 114 (1954).

(6) F. Krafft and W. Vorster, *Chem. Ber.*, **26**, 2815 (1893).

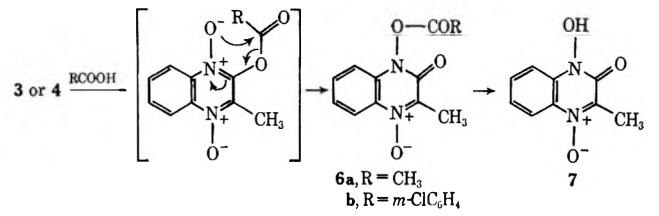
(7) H. J. Backer, *Recl. Trav. Chim., Pays-Bas*, **71**, 409 (1952).

and 90% yields, respectively. These compounds are known to originate, by disproportionation,[8] from the unstable benzenesulfenic acid initially formed.

When the sulfone **4a** was dissolved in glacial acetic acid at room temperature, a new compound was formed in 40% yield which was not the expected 2-acetoxy product but rather 1-acetoxy-3-methylquinoxalin-2-one 4-oxide (**6a**). The characterization of **6a** was based upon its ir spectrum, which showed two carbonyl absorptions at 5.5 and 5.8 μ. The nmr spectrum had signals for two methyl singlets at δ 2.5 and 2.58 but did not have the usual aromatic A_2B_2 multiplet. Instead it had two separate one-proton quartets (J = 7.5, 2.0 Hz) at δ 7.7 and 8.3 assigned to protons at C-8 and C-5, respectively, and a multiplet for the two remaining protons (δ 7.15–7.5). Upon heating the sulfoxide **3a** with acetic acid, two products were obtained, namely the acetate **6a** and its hydrolysis product **7**, in 13 and 44% yields, respectively. Similar results were obtained during the preparation of the sulfone **4b**. Heating the sulfide **2b** with MCPBA in chloroform resulted in the formation of **6b**, presumably from the reaction of the sulfone with *m*-chlorobenzoic acid. The use of pH 7.5 phosphate buffer as part of a two-phase system allowed the successful isolation of **4b**.

Similar arguments can be used to explain the action of organic acids on these compounds. Initial formation of the 2-acyloxy derivative followed by acyl migration to the *N*-oxide oxygen results in **6**, whose hydrolysis affords **7** (Scheme III). Transacylation

SCHEME III



6a, R = CH_3
b, R = *m*-ClC_6H_4
7

involving other forms of *N*-oxides have recently appeared. Shemyakin and coworkers reported acetyl migrations to aldonitrones[9] and transtosylation in the thermal rearrangement of β-phenyl azoxytosylates.[10] Skramstad proposed a similar mechanism to explain the migration of an acetyl group to the oxygen of a nitro group.[11]

Several analogies for the reactions of sulfones with aqueous acid are known.[12] In the case of sulfoxides, however, only one such reaction has been found, which involves the acid hydrolysis of 2-methylsulfinyladenine 1-oxide to isoguanine 1-oxide.[13]

The above reactions, therefore, provide an attractive method for the preparation of 2-haloquinoxaline 1,4-dioxides, which can be used as intermediates for the synthesis of other classes of quinoxaline 1,4-dioxides, *e.g.*, 2-amino-, 2-alkoxy-, etc., not easily accessible by existing methods.

(8) N. Kharasch, "Organic Sulfur Compounds," Vol. I, Pergamon Press, New York, N. Y., 1961, p 392.

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(10) L. A. Neiman, V. S. Smolyakov, Yu. S. Nekrasov, and M. M. Shemyakin, *Tetrahedron*, **26**, 4963 (1970).

(11) J. Skramstad, *Tetrahedron Lett.*, 955 (1970).

(12) See, for example (a) C. W. Noell and R. K. Robins, *J. Amer. Chem. Soc.*, **81**, 5997 (1959); (b) M. Saneyoshi and M. Ikehara, *Chem. Pharm. Bull.*, **16**, 1390 (1968).

(13) R. M. Cresswell and G. B. Brown, *J. Org. Chem.*, **28**, 2560 (1963).

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover capillary apparatus. Nmr spectra were obtained on a Varian A-60 instrument. Mass spectral data were recorded on a Perkin Elmer RMV-65 mass spectrometer. The commercially available MCPBA is 88% pure, and was used as such without purification. All evaporations were conducted *in vacuo* using a water aspirator.

2-Methyl-3-methylthioquinoxaline 1,4-Dioxide (2a).—Acetonylmethyl sulfide (30 g, 0.3 mol) and BFO (40 g, 0.3 mol) were dissolved in methanol (200 ml) and ammonia gas was bubbled in for 10 min. The reaction mixture was allowed to stand at room temperature overnight. The crystalline precipitate was filtered off and washed with methanol. The dried residue weighed 30 g. Crystallization from methanol gave the analytical sample, mp 146–148°, nmr ($CDCl_3$) δ 2.85 (s, 3), 2.95 (s, 3).

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.01; H, 4.50; N, 12.61. Found: C, 53.80; H, 4.52; N, 12.49.

2-Methylthio-3-phenylquinoxaline 1,4-Dioxide (2b).—Acetonylphenyl sulfide (8.3 g, 0.05 mol) and BFO (6.8 g, 0.05 mol) were dissolved in methanol (75 ml) and ammonia gas was bubbled in for 5 min. The product (7.0 g) was isolated and crystallized from methanol–chloroform, mp 153–154°, nmr ($CDCl_3$) δ 2.85 (s, 3).

Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.37; H, 4.23; N, 9.86. Found: C, 63.26; H, 4.11; N, 10.12.

2-Methyl-3-methylsulfinylquinoxaline 1,4-Dioxide (3a).—A solution of MCPBA (2.0 g, 5 mmol) in chloroform (15 ml) was added to an ice-cold solution of the sulfide **2a** (1.1 g, 5 mmol) in chloroform (10 ml) and the reaction mixture was stirred at room temperature overnight. The chloroform solution was washed with aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and evaporated to the finished product (1.2 g). Crystallization from methanol–chloroform furnished the analytical sample, mp 201–202°, nmr ($CDCl_3$) δ 2.92 (s, 3), 3.25 (s, 3).

Anal. Calcd for $C_{10}H_{10}N_2O_3S$: C, 50,42; H, 4.20; N, 11.76. Found: C, 50.27; H, 4.25; N, 11.83.

2-Methyl-3-phenylsulfinylquinoxaline 1,4-Dioxide (3b).—An identical procedure with that used in the preparation of **3a** was followed using the sulfide **2b** (7.0 g, 24 mmol) and MCPBA (5.1 g, 24 mmol). The product obtained weighed 8.6 g, and was crystallized from methanol–chloroform, mp 164–165°, nmr ($CDCl_3$) δ 2.9 (s, 3).

Anal. Calcd for $C_{15}H_{12}N_2O_3S$: C, 60.00; H, 4.00; N, 9.33. Found: C, 60.11; H, 4.25; N, 9.30.

2-Methyl-3-methylsulfonylquinoxaline 1,4-Dioxide (4a).—A solution of MCPBA (4.0 g, 10 mmol) in chloroform (30 ml) was added dropwise to an ice-cold solution of the sulfide **2a** (1.1 g, 5 mmol) in chloroform (15 ml), and the reaction mixture was stirred at room temperature overnight. Similar work-up to that used for the preparation of **3a** furnished the product (1.22 g). The analytical sample was obtained by crystallization from methanol–chloroform, mp 153–154°, nmr ($CDCl_3$) δ 2.92 (s, 3), 3.6 (s, 3).

Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.94; N, 11.02. Found: C, 47.05; H, 3.90; N, 10.97.

2-Methyl-3-phenylsulfonylquinoxaline 1,4-Dioxide (4b).—The sulfide **2b** (2.0 g, 7 mmol) was dissolved in chloroform (100 ml) and was added to phosphate buffer (pH 7.5, 100 ml). A solution of MCPBA (4.25 g, 21 mmol) in chloroform (50 ml) was added to the cooled two-phase system dropwise with vigorous stirring overnight. Thin layer chromotography on silica gel (1:1 EtOAc–benzene) indicated the presence of the desired product with small amounts of **6b**. Similar work-up to that of **4a** furnished the product (1.5 g), which is very sensitive to light. Crystallization from methanol–chloroform furnished the analytical sample, mp 180–181°.

Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.96; H, 3.79; N, 8.86. Found: C, 56.74; H, 3.70; N, 8.58.

2-Chloro-3-methylquinoxaline 1,4-Dioxide (5a).—The procedure described here for the conversion of **3b** to **5a** applies to all other sulfoxides and sulfones. The sulfoxide **3b** (2.0 g, 8.4 mmol) was dissolved in concentrated hydrochloric acid (10 ml). The solution was warmed up on the steam bath for few minutes. An

oily layer separated at the bottom of the reaction flask which was taken up in ether. Drying and evaporation gave an oil (0.7 g). The aqueous acidic layer was diluted with water (75 ml), precipitating the product (1.5 g). The analytical sample was obtained from methanol, mp 166–168°, nmr ($CDCl_3$) δ 2.80 (s, 3), M^+ 212 and 210.

Anal. Calcd for $C_9H_7N_2O_2Cl$: C, 51.30; H, 3.32; N, 13.25. Found: C, 51.32; H, 3.35; N, 13.38.

Thin layer chromotographc analysis of the above oil on silica gel (benzene) showed it to be a mixture of two compounds. Column chromotography (silica gel, 20 g) was used for their separation. Elution with hexane (300 ml) furnished diphenyl disulfide, mp 59–60° (0.28 g). Further elution with a 1:1 mixture of benzene–hexane (700 ml) gave *S*-phenyl benzenethiosulfonate (0.38 g) as a low-melting solid, mp 41–42°.

2-Bromo-3-methylquinoxaline 1,4-Dioxide (5b).—This compound was obtained using 48% HBr solution following the same procedure described for the preparation of **5a**. Crystallization from methanol–chloroform furnished the analytical sample, mp 163–164°, nmr ($CDCl_3$) δ 2.87 (s, 3), M^+ 256 and 254.

Anal. Calcd for $C_9H_7N_2O_2Br$: C, 42.35; H, 2.74; N, 10.98. Found: C, 42.12; H, 2.83; N, 11.03.

1-Acetoxy-3-methylquinoxaline-2-one 4-Oxide (6a). A.—The sulfone **4a** (1.0 g, 4 mmol) was dissolved in acetic acid (25 ml) and was allowed to stand at room temperature for 18 hr. Dilution with water (250 ml) was followed by extraction with chloroform. The chloroform layer was backwashed with water, dried over magnesium sulfate, filtered, and evaporated to dryness to give a gum (0.37 g). The analytical sample was obtained by crystallization from ether–chloroform without the use of heat, mp 142–143°, nmr ($CDCl_3$) δ 2.5 (s, 3), 2.57 (s, 3).

Anal. Calcd for $C_{11}H_{10}O_4N_2$: C, 56.41; H, 4.27; N, 11.96. Found: C, 56.38; H, 4.49; N, 11.77.

B.—The sulfoxide **3a** (2.5 g, 10 mmol) was dissolved in acetic acid (25 ml) by heating for 0.5 hr. Dilution with water (250 ml) was followed by extraction with chloroform. A similar work-up to that above gave a gum (1.9 g). This was chromatographed on Florisil eluting first with chloroform (400 ml) to give **6a** (0.32 g), followed by a 1:1 mixture of methanol–chloroform (500 ml) to furnish the hydroxamic acid **7** (1.0 g), mp 224–225°, identical with an authentic sample.[4]

1-*m*-Chlorobenzoxy-3-methylquinoxalin-2-one 4-Oxide(6b).—The sulfide **2b** (2.0 g, 7 mmol) was dissolved in chloroform (100 ml). To this solution MCPBA (2.83 g, 14 mmol) in chloroform (50 ml) was added and the resulting mixture was refluxed for 1 hr. One more equivalent of MCPBA (1.4 g) was added and the reaction mixture was refluxed for an additional 1 hr. The chloroform solution was first washed with a saturated solution of sodium bicarbonate (3 × 50 ml), and then with water, dried, filtered, and evaporated to dryness to yield a solid. The solid residue (0.6 g) was crystallized from methylene chloride–ether, mp 161–162°, nmr ($CDCl_3$) δ 2.6 (s, 3), M^+ 332 and 330.

Anal. Calcd for $C_{16}H_{11}N_2O_4Cl$: C, 58.09; H, 3.32; N, 8.47. Found: C, 57.98; H, 3.23; N, 8.40.

Acknowledgment.—The author wishes to thank Mr. Leo B. Keith, Jr., for his technical assistance.

Registry No.—**2a**, 39576-50-6; **2b**, 39576-56-2; **3a**, 39576-76-6; **3b**, 40735-40-8; **4a**, 39576-77-7; **4b**, 40735-42-0; **5a**, 39576-78-8; **5b**, 39576-79-9; **6a**, 40735-45-3; **6b**, 40735-46-4.

O-Nitrene and *O*-Nitrenium Cation Intermediates in Reactions of O-Substituted Hydroxylamines[1]

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Two methods were investigated for the generation of *O*-nitrenes (**3**) and/or *O*-nitrenium cations (**4**): lead tetraacetate oxidation of *O*-alkylhydroxylamines (**5**) and thermal base-catalyzed decomposition of *N*-*p*-toluenesulfonyl-*O*-alkylhydroxylamines (**6**). Lead tetraacetate oxidation of *O*-diphenylmethylhydroxylamine (**5a**) was solvent dependent and afforded mixtures of products containing *O*-diphenylmethylbenzophenone oxime, benzophenone, benzhydrol, and products corresponding to net O to N migration of Ph_2CH–, *N*-diphenylmethoxy-*N'*-diphenylmethyldiazine *N'*-oxide (**9**), and benzophenone oxime. *p*-Nitrobenzyl alcohol was the only product formed on oxidation of *O*-*p*-nitrobenzylhydroxylamine (**5b**) with lead tetraacetate. The stereochemical course of formation of *N*-alkoxyaziridines from lead tetraacetate oxidation of *O*-*n*-butylhydroxylamine in the presence of *cis*- and *trans*-2-butene was examined and found to be nonstereospecific. *trans*-2-Butene afforded *N*-*n*-butoxy-*trans*-2,3-dimethylaziridine (**12**) and *N*-*n*-butoxy-*cis*-2,3-dimethylaziridine (**13**) in an 82:18 ratio while the **12**:**13** ratio from *cis*-2-butene was 38:62. The dominant thermal reaction from **6** and sodium hydride involved O–N bond cleavage. Thus **6a** and excess sodium hydride gave benzhydrol as the major product which was shown to arise *via* cleavage of the carbanion of **6a** to benzophenone and *p*-toluenesulfonamide anion followed by reduction of benzophenone to benzhydrol. O to N migration was observed when either *n*-butyllithium or only small excesses of sodium hydride were used to yield benzophenone oxime (quantitative from *n*-butyllithium). No O to N migration was observed using **6c** or **6d** and NaH with the products being *p*-bromobenzoic acid and *p*-methoxybenzoic acid, respectively, probably arising *via* oxidation of the corresponding aldehydes. The suggestion is made that there is, as yet, no conclusive evidence for the intermediacy of **3** in any reactions of O-substituted hydroxylamines or its derivatives. Mechanisms not involving *O*-nitrenes are suggested including the possibility of organolead intermediates being the species undergoing O to N migration and addition to olefins in the lead tetraacetate oxidations, and fragmentation–recombination pathways for the base-catalyzed reactions of **6a**.

Species possessing an electron-deficient nitrogen have been proposed and, in some instances, detected as reactive intermediates in a great many organic reactions.[2] Even-electron intermediates of this type may be either nitrenes ($R\ddot{N}$:) or nitrenium ions (R^+-$\ddot{N}R'$), and each of these may exist either in a singlet or triplet electronic state with the triplet usually being lower in energy.[2c,3] If substituents are chosen so as to be able to interact electronically with the unfilled 2p orbital on nitrogen, the energy levels of the singlet and triplet states will be perturbed so that the singlet could become the ground state, *e.g.*, when R or R′ is nitrogen, oxygen, or fluorine. With

(1) Portions of the work described here have been reported previously: (a) F. A. Carey, 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967, paper 69; (b) F. A. Carey and L. J. Hayes, *J. Amer. Chem. Soc.*, **92**, 7613 (1970).

(2) (a) P. A. S. Smith in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963; (b) J. H. Boyer in "Mechanisms of Molecular Migrations," Vol. 2, B. S. Thyagarajan, Ec., Interscience, New York, N. Y., 1969; (c) P. G. Gassman, *Accounts Chem. Res.*, **3**, 26 (1970); (d) P. A. S. Smith, "Open-Chain Nitrogen Compounds," W. A. Benjamin, New York, N. Y., 1965.

(3) R. S. Berry in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, Chapter 2.

respect to this point *ab initio* SCF–CI calculations on NH_2^+ indicate the triplet to be *ca.* 45 kcal/mol lower in energy than the singlet,[4] while it has been suggested that NF_2^+ has a singlet ground state.[5] For nitrenes CNDO–INDO calculations indicate singlet ground states for both HON and H_2NN.[6]

N-Nitrenes (**1**, diazenes, azanitrenes) and *N*-nitrenium ions (**2**, diazenium, azanitrenium) are sufficiently

$R_2N\ddot{N}$ (**1**) $\qquad R_2N\overset{+}{\ddot{N}}H$ (**2**)

stabilized to be accessible by chemical means, have been the object of a number of investigations, and are known to be important in reactions of hydrazine and its derivatives.[7]

The analogous oxygen-stabilized species, *O*-nitrenes (**3**, oxyazenes, oxynitrenes) and *O*-nitrenium ions (**4**,

$RO\ddot{N}$ (**3**) $\qquad RO\overset{+}{\ddot{N}}H$ (**4**)

oxyazenium, oxynitrenium), have proved to be more elusive. This paper reports the results of numerous attempts o generate **3** and **4** by applying the techniques which had been shown to be useful for generation of **1** and **2**.

When these studies were begun there were no published reports of systematic attempts at generating **3** and **4**, although the possibility of an *O*-nitrene intermediate intervening in the oxidation of *O*-alkylhydroxylamines to yield hyponitrite esters had been noted.[2d]

During the course of this work several reports appeared which described attempts to generate **3** or postulated it as an intermediate.[8] *A priori*, **3** and **4** should be higher energy intermediate than **1** and **2** and presumably more difficult to generate, since oxygen is less effective at stabilizing an adjacent electron-deficient center than is nitrogen.

Results

Of the techniques which can be considered conventional for generation of nitrenes and related electron-deficient intermediates, two were chosen for detailed examination with respect to the question of *O*-nitrenes: (a) oxidation of *O*-alkylhydroxylamines (**5**) (eq 1) and (b) base-promoted α-elimination of *N*-sulfonyl-*O*-alkylhydroxylamines (**6** or **7**) (eq 2).

The required substrates for each process, *O*-alkylhydroxylamines (**5a–e**) and their corresponding sulfonamide derivatives (**6**, **7**), were conveniently available using standard synthetic routes.

$RONH_2$ (**5**)

5a, R = Ph_2CH
b, R = p-$O_2NC_6H_4CH_2$
c, R = CH_3
d, R = $CH_3CH_2CH_2CH_2$
e, R = $PhCH_2$
f, R = p-$ClC_6H_4CH_2$

$RONHSO_2$–C_6H_4–CH_3 (**6**)

6a, R = Ph_2CH
b, R = $PhCH_2$
c, R = p-$BrC_6H_4CH_2$
d, R = p-$CH_3OC_6H_4CH_2$

$RONHSO_2CH_3$ (**7**)

7a, R = Ph_2CH

$$RONH_2 \xrightarrow{[O]} RO\ddot{N}: \qquad (1)$$

(**5**)

$$RONHSO_2R' \xrightarrow{\text{base}} RO\bar{N}SO_2R' \xrightarrow{\Delta} RO\ddot{N} + RSO_2^- \qquad (2)$$

(**6**)

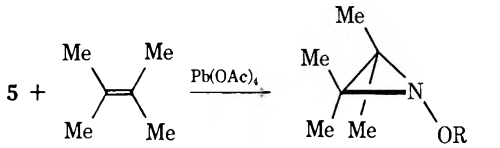
Oxidation of *O*-Substituted Hydroxylamines.—A number of oxidizing agents were briefly surveyed using *O*-diphenylmethylhydroxylamine (**5a**) as the substrate. Nickel peroxide,[9] a source of hydroxyl radicals reported to oxidize amines to nitrenes, reacted rapidly with **5a** to cleave the O–N bond, yielding benzhydrol in 83% yield. *N*-Bromosuccinimide in carbon tetrachloride converted **5a** to benzophenone (29%) and *O*-diphenylmethylbenzophenone oxime ($Ph_2CHON{=}CPh_2$, **8**, 51%), presumably formed by condensation of **5a** with benzophenone. Mercuric oxide, a commonly used oxidant of *N*,*N*-dialkylhydrazines,[10] failed to react with **5a**.

Lead tetraacetate reacted readily with **5a**, as well as other *O*-alkylhydroxylamines, to afford product mixtures the composition of which was solvent dependent. In dichloromethane at 25°, **5a** yielded a white, crystalline solid formulated on the basis of nmr[11] and ir[12] data as *N*-diphenylmethoxy-*N'*-diphenylmethyldiazine *N'*-oxide [$Ph_2CHON{=}N(O^-)CHPh_2^+$, **9**] in 32% yield. This product was also isolated from lead tetraacetate oxidation of **5a** in trichloroethylene as solvent. Complex reaction mixtures containing benzophenone, benzhydrol, and either benzhydryl acetate or benzhydryl methyl ether were obtained in acetic acid and methanol, respectively. When **5a** was oxidized with lead tetraacetate in pyridine or dimethylformamide there was formed, in addition to benzophenone and **8**, small amounts of benzophenone oxime. The lead tetraacetate oxidation of *O*-*p*-nitrobenzylhydroxylamine was relatively clean and gave *p*-nitrobenzyl alcohol as the only product in high yield.

Since Brois[8c] had reported that oxidation of *O*-methylhydroxylamine (**5c**) in the presence of tetramethylethylene resulted in the formation of the *N*-methoxyaziridine **10**, a number of oxidations were carried out in the presence of olefins as trapping reagents.

For reasons of convenience we chose to use *O*-*n*-butylhydroxylamine (**5d**) and found that this compound afforded the *N*-*n*-butoxyaziridine (**11**) in 40% yield on oxidation with lead tetraacetate in tetramethylethylene.

(4) S. T. Lee and K. Morokuma, *J. Amer. Chem. Soc.*, **93**, 6863 (1971).
(5) A. B. Cornford, D. C. Frost, F. G. Herring, and C. A. McDowell, *J. Chem. Phys.*, **54**, 1872 (1971).
(6) (a) L. J. Hayes, F. P. Billingsley, II, and C. Trindle, *J. Org. Chem.*, **37**, 3924 (1972); (b) J. Peslak, Jr., D. S. Klett, and C. W. David, *J. Amer. Chem. Soc.*, **93**, 5001 (1971).
(7) D. M. Lemal in "Nitrenes," W. Lwowski, Ed., Interscience, New York, N. Y., 1970, Chapter 10; D. M. Lemal, F. Menger, and E. Coats, *J. Amer. Chem. Soc.*, **86**, 2395 (1964).
(8) (a) J. H. Boyer and J. D. Woodyard, *J. Org. Chem.*, **33**, 3329 (1968); (b) A. Hassner, R. Wiederkehr, and A. J. Kascheres, *ibid.*, **35**, 1962 (1970); (c) S. L. Brois, *J. Amer. Chem. Soc.*, **92**, 1079 (1970); (d) R. Partch, B. Stokes, D. Bergman, and M. Budnik, *Chem. Commun.*, 1504 (1971); (e) R. O. C. Norman, R. Purchase, and C. B. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1701 (1972); (f) B. V. Ioffe and E. V. Koroleva, *Zh. Org. Khim.*, **8**, 1548 (1972); *Tetrahedron Lett.*, 619 (1973).
(9) (a) K. Nakagawa, R. Konaka and T. Nakata, *J. Org. Chem.*, **27**, 1597 (1962); (b) K. Nakagawa and H. Onoue, *Tetrahedron Lett.*, 1433 (1965).
(10) See, for example, C. G. Overberger and S. Altscher, *J. Org. Chem.*, **31**, 1728 (1966); P. S. Forgione, G. S. Sprague, and H. J. Troffkin, *J. Amer. Chem. Soc.*, **88**, 1079 (1966).
(11) J. P. Freeman, *J. Org. Chem.*, **28**, 2508 (1963).
(12) M. V. George, R. W. Kierstead, and G. F. Wright, *Can. J. Chem.*, **37**, 679 (1959).



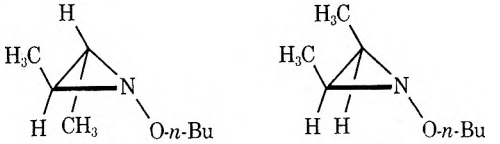
10, R = CH_3
11, R = $CH_3CH_2CH_2CH_2$

The nmr spectrum of **11** exhibited two singlets at δ 1.15 and 1.19 of equal intensity for the aziridine ring methyl groups which are nonequivalent by virtue of the slow rate of pyramidal inversion at nitrogen.[3c]

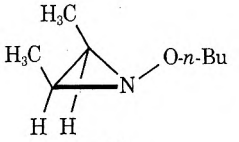
Since an important piece of evidence in deducing the nature of the intermediate formed by lead tetraacetate oxidation of O-substituted hydroxylamines is whether the intermediate reacts with olefin to afford aziridines in a concerted or nonconcerted fashion, it was considered important to try to trap the intermediate with *cis*- and *trans*-2-butene. Generally speaking, stereospecific addition to *cis*- and *trans*-2-butene is taken as supporting concerted addition, although a nonconcerted addition can be stereospecific. Nonstereospecific addition, however, requires that the process not be concerted.

When the necessary reactions were performed two observations were made. First, both *cis*-2-butene and *trans*-2-butene were much less effective at trapping the reactive intermediate than tetramethylethylene, giving yields of less than 20% of *N*-*n*-butoxyaziridines. Secondly, the *reactions were not stereospecific*. Thus, addition of a solution of **2b** in dichloromethane to a well-stirred slurry of lead tetraacetate in *trans*-2-butene at −78° afforded *N*-*n*-butoxy-*trans*-2,3-dimethylaziridine (**12**) and *N*-*n*-butoxy-*cis*-2,3-dimethylaziridine (**13**) in a ratio of 82:18. Using *cis*-2-butene as the trap under identical conditions gave **12** and **13** in a ratio of 38:62. Control experiments demonstrated that neither the *cis*- and *trans*-2-butene nor the products isomerized under the reaction conditions.

Assignment of structure to the adducts was made by considering their nmr spectra. The isomer with the shorter retention time on glpc (1.7 min) was identified as **12** by the presence of two nonequivalent methyl doublets at δ 1.13 (J = 5 Hz) and 1.33 (J = 5 Hz). The isomer with the longer retention time (2.2 min) exhibited a single methyl peak at δ 1.11 (doublet, J = 6 Hz) consistent with **13**. The other cis isomer **14**



12 **13**



14

did not appear to be present. Both **12** and **13** gave similar mass spectra with *m/e* 70 as the most intense peak in each, corresponding to loss of BuO· from the molecular ion to leave $(C_4H_8N)^+$. The next most intense peak in each was *m/e* 41, while *m/e* 143 (parent) was observed to be of quite low intensity (1.1 and 2.8%).

Base-Promoted Decomposition of *N*-Sulfonyl-*O*-alkylhydroxylamines.—Conversion of **6a** or **7a** to the corresponding sodium or lithium salt with sodium hydride or *n*-butyllithium, respectively, followed by pyrolysis in triglyme at 160-200° resulted in the loss of sulfinate and net O to N migration of the diphenylmethyl substituent to afford benzophenone oxime. These results are summarized in Table I and eq 3.

6a or **7a** → $Ph_2CHONSO_2X$ → $Ph_2C{=}NOH + XSO_2^-$ (3)

TABLE I

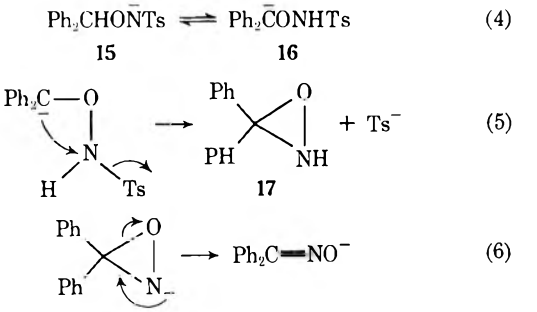
THERMAL DECOMPOSITION OF ANIONS DERIVED FROM **6a** AND **7a**

Substrate	Base	Leaving group	Yield of $Ph_2C{=}NOH$, %
6a	NaH (2 equiv)	Ts^-	58
7a	NaH (2 equiv)	$CH_3SO_2^-$	48
6a	BuLi (1.1 equiv)	Ts^-	100

When large excesses of NaH were employed the reaction took a different course and produced benzhydrol exclusively.

Although the reaction was chosen as one likely to produce an *O*-nitrene and the formation of benzophenone oxime is consistent with the anticipated behavior of such an intermediate, there do exist a number of alternative mechanisms which could afford benzophenone oxime without an *O*-nitrene being involved. Efforts were made to test the more reasonable possibilities by experiment.

One such possibility for the case of **6a** is shown in eq 4–6. This scheme assumes that the expected



(4)

15 **16**

(5)

17

(6)

anion **15** is in equilibrium with the carbanion **16**, which undergoes an intramolecular displacement of *p*-toluenesulfinate to afford the oxazirane **17**, which in turn rearranges to benzophenone oxime.

This sequence of events is analogous to one tentatively suggested by Paquette to explain the O to N migration observed in the base-catalyzed decomposition of *N*-chloro-O-substituted hydroxylamines.[13]

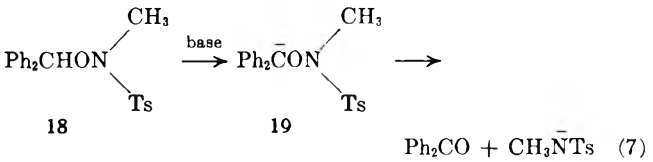
This possibility could not be tested directly using **6a** but rather required the *N*-methyl compound **18**. If the carbanion → oxazirane transformation is important, then **18** should undergo this as readily as **6a** and lead to products derived from *N*-methyldiphenyloxazirane.[14] Treatment of **18** with 2 equiv of sodium hydride in triglyme at 200° for 19 hr and separation of

(13) L. A. Paquette, *Tetrahedron Lett.*, 485 (1962).

(14) For a review of oxazirane chemistry see W. D. Emmons in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part One, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, Chapter IV.

the products by preparative tlc led to the isolation of benzophenone (13%), benzhydrol (72%), and *N*-methyl-*p*-toluenesulfonamide (46%). These products are most reasonably explained as arising from cleavage of the carbanion derived from **18** to benzophenone and *N*-methyl-*p*-toluenesulfonamide followed by reduction of the benzophenone to benzhydrol by sodium hydride.[15]

Evidence to support the notion that the benzhydrol is formed by reduction of the benzophenone resulting from cleavage of the carbanion was obtained by repeating the experiment using **18** substituted with deuterium at the carbon atom which bears the two phenyl groups. The benzhydrol formed in this reaction was isolated in 65% yield and determined to have lost completely its deuterium label in accordance with the prediction based on eq 7.



18 19

$$Ph_2CO + CH_3\bar{N}Ts \quad (7)$$

It thus appears that carbanions in these systems, when generated, undergo efficient fragmentation to carbonyl compounds rather than intramolecular O to N rearrangement. This also served to explain the results of reactions in which the *p*-toluenesulfonamide derivatives **6b–d** of *O*-benzyl-, *O*-*p*-bromobenzyl-, and O-*p*-methoxybenzylhydroxylamine were treated with sodium hydride in triglyme at elevated temperature. The products were those formed by cleavage of the oxygen–nitrogen bond, affording initially substituted benzaldehydes and *p*-toluenesulfonamide. The isolated products from **6b**, **6c**, and **6d**, exclusive of *p*-toluenesulfonamide, were benzoic acid (30%), *p*-bromobenzoic acid (41%), and *p*-methoxybenzoic acid (39%), respectively. In one experiment benzonitrile was isolated from **6b** in 35% yield along with a small amount (8%) of *N*-*p*-toluenesulfonylbenzylamine. Both the conversion of benzaldehyde to benzoic acid and the formation of $PhCH_2NHTs$ were established as occurring under the reaction conditions by a control experiment in which the anion of *p*-toluenesulfonamide was generated using sodium hydride and heated in triglyme with benzaldehyde to yield benzoic acid (48%), benzyl alcohol (15%), and *N*-*p*-toluenesulfonylbenzylamine (11%).

The dominant reaction path of **6b**, **6c**, and **6d** therefore appears to be base-catalyzed cleavage to aldehyde and *p*-toluenesulfonamide anion. The formation of *N*-*p*-toluenesulfonylbenzylamine probably results from condensation of these two fragments followed by dehydration and reduction of the tosylimine with sodium hydride as formulated in Scheme I.

It is reasonable that PhCH=NTs is also the precursor to benzonitrile *via* base-catalyzed β-elimination, although benzonitrile was not observed in the control experiment. It is not known exactly how oxidation of the aldehyde to the carboxylic acid occurs, and speculation on that point will not be offered, since it is not essential to the central question, *i.e.*, whether *O*-nitrenes are formed in these reactions.

(15) F. W. Swamer and C. R. Hauser, *J. Amer. Chem. Soc.*, **68**, 2647 (1946).

SCHEME I

$$PhCH_2\bar{O}NTs \rightleftharpoons PhCHONHTs \longrightarrow PhCHO + Ts\bar{N}H$$

$$PhCHO + Ts\bar{N}H \longrightarrow PhCH(NHTs)O^-$$

$$PhCH(NHTs)O^- \rightleftharpoons PhCH(\bar{N}Ts)OH \longrightarrow PhCH{=}NTs$$

$$PhCH{=}NTs \xrightarrow{\text{reduction}} PhCH_2NHTs$$

Discussion

It is apparent that many of the experimental methods which are suitable for the generation of *N*-nitrenes (**1**) from hydrazine derivatives are not directly applicable to the generation of *O*-nitrenes (**3**) from hydroxylamine derivatives. The most common observation in reactions of *O*-alkylhydroxylamines and their derivatives is cleavage of the O–N bond. This has been observed previously, for example, in the attempted deoxygenation of benzyl nitrite and *tert*-butyl nitrite by trivalent phosphorus compounds as a route to **3**.[8a] Oxidation of **5e** with chromic acid[16] or bromine afforded mixtures of benzaldehyde and benzyl alcohol with the bromine oxidation having been shown[17] to proceed by initial formation of a hyponitrite ester,[18] which undergoes fragmentation to nitrogen and alkoxy radicals which in turn disproportionate to an aldehyde and an alcohol.[19] The formation of the hyponitrite ester need not involve the intermediacy of **3**, since a reasonable alternative path exists. The overall process can be represented by Scheme II for the case of **5e**.

SCHEME II

$$\mathbf{5e} + Br_2 + OH^- \longrightarrow PhCH_2ONHBr + H_2O + Br^-$$

$$PhCH_2ONHBr + \mathbf{5e} + OH^- \longrightarrow PhCH_2ONHNHOCH_2Ph + Br^- + H_2O$$

$$PhCH_2ONHNHOCH_2Ph + Br_2 + 2OH^- \longrightarrow PhCH_2ON{=}NOCH_2Ph + 2H_2O + 2Br^-$$

$$PhCH_2ON{=}NOCH_2Ph \longrightarrow N_2 + 2PhCH_2O\cdot$$

$$2PhCH_2O\cdot \longrightarrow PhCHO + PhCH_2OH$$

Cleavage of the O–N bond was the dominant reaction course in most of the reactions carried out in this study as well. It was not considered significant for our purposes to determine whether hyponitrite esters were involved in these processes, because, as in the example cited above, hyponitrite ester formation does not require an *O*-nitrene to be present as its precursor.[20] The more important concerns were those reactions which afforded products having the O–N bond intact. In the case of lead tetraacetate oxidation of **5** these were the formation of nitroso compounds (as dimers) from **5e** and **5f**,[8d,e] the formation of **9** from **5a**, and the formation of *N*-alkoxyaziridines when the oxidation of **5c**[8c] and **5d** was performed in the presence of olefins.

While O to N migration of an aralkyl group to afford a nitroso compound is consistent with the anticipated

(16) R. Kothe, *Justus Liebigs Ann. Chem.*, **266**, 310 (1891).

(17) L. Seed, British Patent 795,824; *Chem. Abstr.*, **53**, 219 (1959).

(18) For a review on hyponitrite esters see M. N. Hughes, *Quart. Rev., Chem. Soc.*, **22**, 1 (1968).

(19) S. K. Ho and J. B. DeSousa, *J. Chem. Soc.*, 1788 (1961); H. Kiefer and T. G. Traylor, *Tetrahedron Lett.*, 6163 (1966); C. Walling and J. A. McGuiness, *J. Amer. Chem. Soc.*, **91**, 2053 (1969).

(20) See ref 8e for a plausible mechanistic scheme to rationalize formation of dibenzyl hyponitrite in the lead tetraacetate oxidation of **5e**.

behavior of an *O*-nitrene, the observation of products resulting from O to N migration does not demand the intermediacy of **3**. The most probable initial reaction of **5** with lead tetraacetate is formation of the organolead intermediate **20**.

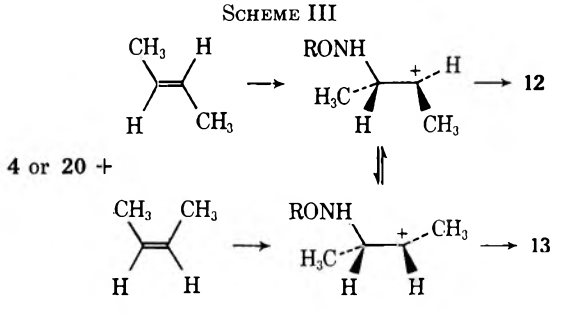
$$\mathbf{5} + Pb(OAc)_4 \longrightarrow \underset{\mathbf{20}}{RONHPb(OAc)_3} + HOAc \qquad (8a)$$

By analogy[21] with other reactions of organolead intermediates, **20** could be expected to serve as a source of the *O*-nitrenium ion **4**, with **3** resulting from deprotonation of **4**.

$$\mathbf{20} \longrightarrow \underset{\mathbf{4}}{RO\overset{+}{N}H} + Pb(OAc)_2 + OAc^- \qquad (8b)$$

The *O*-nitrenium cation **4** seemingly has the capacity to do all of the things anticipated for **3**: O to N migration of R and addition to alkenes are very likely reactions of **4**. Additionally, these reactions could occur in a manner concerted with cleavage of the nitrogen–lead bond of **20**. The available data do not allow a choice to be made regarding the point at which reactions occur during the process **20** → **4** → **3**, and the conclusion that **3** and/or **4** are intermediates in the lead tetraacetate oxidation of O-substituted hydroxylamines is not warranted. This conclusion receives support from the lack of stereospecificity observed in *N*-alkoxyaziridine formation from *cis*- and *trans*-2-butene and **5d**. Formation of *N*-alkoxyaziridine is not nearly so efficient as from tetramethylethylene and the total amount formed is not large, being estimated at 10–20%. Nevertheless, both **12** and **13** are formed (in different amounts) from each olefin, providing evidence that at least a portion of the adduct arises by a nonstereospecific process. Triplet *O*-nitrene is not a reasonable intermediate, because calculations[6a] indicate the singlet *O*-nitrene to be more stable than the triplet and the reaction conditions are those which because of spin conservation would not be expected to yield the triplet state directly. Nonstereospecific addition requires at least a two-step mechanism and either **20** or **4** could add in a two-step process as shown in Scheme III.

SCHEME III



Complete equilibration of the initial carbonium ion intermediates would not occur if the rate of closure were competitive with the rate of rotation around the carbon–carbon bond. The reaction mixtures were complex, and if pinacol-type rearrangement products were formed they were not detected.

(21) For references and mechanistic discussion of lead tetraacetate oxidations see (a) W. H. Starnes, Jr., *J. Amer. Chem. Soc.*, **90**, 1807 (1968); (b) J. K. Kochi, *Rec. Chem. Progr.*, **27**, 207 (1966); (c) R. Criegee in "Oxidation in Organic Chemistry," Part A, K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, Chapter V.

The results of the base-catalyzed thermal decomposition reactions of *N*-*p*-toluenesulfonyl-*O*-alkylhydroxylamines are similarly inconclusive with regard to the intermediacy of **3**. In most cases the reactions appeared to be those of carbanions formed in equilibrium with the desired amide ions leading to cleavage to an aldehyde or ketone plus *p*-toluenesulfonamide anion. In this respect the reactions of **6** and **7** parallel closely the well-known Wittig rearrangement of *O*-benzyl esters for which a fragmentation–recombination mechanism has been shown to be operative.[22] (Compare Schemes I and IV.)

SCHEME IV

$$ROCH_2Ph \xrightarrow{base} ROCHPh$$

$$ROCHPh \longrightarrow R^- + PhCHO$$

$$R^- + PhCHO \longrightarrow RCHPh \quad (O^-)$$

The condensation of *p*-toluenesulfonamide anion with aldehydes and ketones is not very efficient and alternative reactions, such as reduction by sodium hydride or oxidation (mechanism not known), compete effectively.

The fragmentation–recombination pathway could conceivably lead to benzophenone oxime from **6a** *via* oxazirane **17** formed by condensation of benzophenone and *p*-toluenesulfonamide ion (eq 9).

$$Ph_2C{=}O + TsNH^- \longrightarrow \underset{\mathbf{19}}{Ph_2CNHTs} \longrightarrow \underset{\mathbf{17}}{\text{Ph, O, Ph, NH}} \qquad (9)$$

This possibility was tested by attempting to condense *p*-toluenesulfonamide with benzophenone in the presence of sodium hydride under the conditions of reaction. No benzophenone oxime was obtained. The isolated products were benzhydrol (32%) and recovered benzophenone (36%). Although the results of this control experiment were not supportive of eq 9, we are reluctant to discard this possibility totally, since it is not always possible to ensure that the conditions of a control experiment are identical with those which exist during a reaction. This mechanism fits best into the total picture which emerges for base-catalyzed thermal decomposition of **6** and **7**.

The conclusions to be reached from this study are that the methods used to generate *N*-nitrenes from hydrazine derivatives when applied to the generation of *O*-nitrenes from hydroxylamine derivatives afford results which do not uniquely require the involvement of *O*-nitrenes.

Experimental Section[23]

Reactions of *O*-Diphenylmethylhydroxylamine with Oxidizing Agents. A. Nickel Peroxide.—To a solution of 383 mg (1.92 mmol) of **5a** in 5 ml of dry benzene was added 1.6 g of nickel peroxide.[9a] A rapid reaction occurred with **5a** being entirely consumed within 5 min (tlc examination). The solution was

(22) D. L. Dalrymple, T. L. Kruger, and W. N. White in "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience, New York, N. Y., 1967, Chapter 14.

(23) See paragraph at end of paper regarding supplementary material.

filtered and evaporated to yield 291 mg (83%) of benzhydrol, identified by comparison of its ir spectrum with that of authentic material. After recrystallization from hexane the melting point was 64–65.5° (reported mp 68–69°).[24]

B. *N*-Bromosuccinimide.—A solution containing 386 mg (1.93 mmol) of **5a** and 352 mg (1.93 mmol) of *N*-bromosuccinimide in 5 ml of carbon tetrachloride was refluxed under nitrogen for 20 hr. The solution was filtered and evaporated and the residue was chromatographed on 30 g of Woelm silica gel. Elution with chloroform (100 ml) afforded 178.5 mg (51%) of *O*-diphenylmethyl benzophenone oxime (**8**) as a clear syrup which soon crystallized (identified by comparison of its ir spectrum with that of authentic material). The product on recrystallization from ethanol had mp 96–98.5° (reported mp 101.5–102°).[25]

The second fraction, eluted with 100 ml of 10:1 chloroform–ether, was a syrup (102 mg, 29%) identified as benzophenone by its ir spectrum.

C. Lead Tetraacetate in Methylene Chloride.—To 746 mg (3.75 mmol) of **5a** in 20 ml of methylene chloride was added 1.68 g (3.75 mmol) of lead tetraacetate while stirring at 0°. A vigorous reaction occurred. After 10 min the reaction mixture was worked up and evaporated to leave a syrup which was taken up in ethanol, cooled, and filtered to afford 223 mg of **9** as a tan solid, mp 114–127° (crude yield 32%). Recrystallization from ethanol gave the analytical sample: mp 146.7–147.7°; ir ($CHCl_3$) 3100–3000, 1500, 1460, 1004, 994, 940, 910, 700 cm^{-1}; nmr ($CDCl_3$) δ 7.4 (s, 20, aromatic), 6.45 (s, 1, HCO), 6.35 (s, 1, HCN).

Anal. Calcd for $C_{26}H_{22}N_2O_2$: C, 79.17; H, 5.62; N, 7.10; mol wt, 394.5. Found: C, 79.03; H, 5.62; N, 7.30; mol wt, 375 (Rast).

The same product was formed in 19% yield when the oxidation was carried out in trichloroethylene. In this case the major product was benzhydrol (36%).

D. Lead Tetraacetate in Pyridine.—Lead tetraacetate (1.73 g, 3.9 mmol) was added to 487 mg (2.4 mmol) of **5d** in 5 ml of pyridine. An exothermic reaction occurred. The solution was refluxed for 17 hr (N_2 atmosphere) and worked up. The extracts were evaporated and the pyridine was removed by coevaporation with 50 ml of toluene on the rotary evaporator. The residue was chromatographed on 40 g of Woelm silica gel and eluted first with chloroform, collecting 50-ml fractions. The first three fractions contained 61 mg (14%) of **8**, mp 96–99°, identified by its ir spectrum (lit. mp 101.5–102°).[25] Fractions 4–8 contained 216 mg (48%) of benzophenone identified by its ir spectrum and R_f on tlc. Fractions 9 and 10 contained 81 mg (17%) of benzophenone oxime identified by ir and R_f on tlc.

The same compounds were obtained when the oxidation was carried out in dimethylformamide at 25° for 2 hr. The yield of **8** was 42%, benzophenone was 12%, and the oxime was *ca.* 30% (chromatographic fraction contaminated with benzhydrol).

Reaction of *O*-*p*-Nitrobenzylhydroxylamine with Lead Tetraacetate.—To a solution of 400 mg (2.4 mmol) of **5b** in 5 ml of methanol was added 1.2 g (2.7 mmol) of lead tetraacetate. The reaction mixture was worked up after 20 hr and evaporated to leave 231 mg (69%) of crude *p*-nitrobenzyl alcohol, mp 65–76°, the ir spectrum of which was identical with that of authentic material. Recrystallization from water afforded material of mp 90–92° (lit. mp 93°).[24]

A similar experiment in methylene chloride at 25° for 10 min afforded *p*-nitrobenzyl alcohol in 68% yield.

Reaction of *O*-*n*-Butylhydroxylamine (5d) with Lead Tetraacetate in the Presence of Olefins.—A mixture of lead tetraacetate (6.2 g, 13.9 mmol) and excess olefin was cooled in an isopropyl alcohol–Dry Ice bath while a solution of 1.0 g (11.2 mmol) of **5d** in 20 ml of dichloromethane was added slowly over the course of 1 hr. The reaction mixture was allowed to warm to room temperature and then stirred for an additional 1 hr, during which time a precipitate formed. The reaction mixture was filtered and the precipitate was washed thoroughly with a small amount of dichloromethane. The dichloromethane solution was washed with 5% sodium carbonate and water and dried ($MgSO_4$), and the solvent was distilled at atmospheric pressure to leave the crude product.

A. Tetramethylethylene.—The crude product obtained when **5d** 7 ml (68.5 mmol) of tetramethylethylene was used as the trapping reagent was chromatographed on 50 g of silica gel. Elution with *n*-hexane (200 ml) followed by a 90% *n*-hexane–ether solution (200 ml) yielded 715 mg (37%) of 1-*n*-butoxy-2,2,3,3-tetramethylaziridine (**11**): ir ($CHCl_3$) 2975, 1460, 1380, 1170, 1120, 1070, and 1043 cm^{-1}; nmr ($CDCl_3$) δ 3.65 (t, 2 H, J = 6 Hz), 1.19 (s), 1.15 (s), and 0.7–1.8 (m), the area between 0.7 and 1.8 integrated for 19 H.

The analytical sample was prepared by preparative glpc.

Anal. Calcd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 70.03; H, 12.29; N, 8.14.

The reaction was repeated with 2 ml of acetic acid added to the initial lead tetraacetate–olefin mixture. A 40% yield of the aziridine was obtained.

B. *trans*-2-Butene.—Analysis of the crude product by glpc at a column temperature of 80° and a flow rate of 85 ml/min revealed only two products with retention times greater than 1 min. The major one (retention time 1.7 min) was isolated by preparative glpc and determined to be 1-*n*-butoxy-*trans*-2,3-dimethylaziridine (**12**): ir ($CHCl_3$) 2975, 1740, 1450, 1380, 1250, 1075, 1035, and 970 cm^{-1}; nmr ($CDCl_3$) δ 3.7 (t, 2 H, J = 6.5 Hz) and 0.7–2.0 (m, 15 H); mass spectrum m/e 70 (base peak), M^+ 143, 56, 41.

Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.08; H, 11.82; N, 9.98.

The minor component had the same retention time (2.2 min) as 1-*n*-butoxy-*cis*-2,3-dimethylaziridine (**13**). Sufficient material was trapped from the glpc to measure the ir spectrum of this product. It was identical with that of **13**.

The ratio of trans (**12**) to cis (**13**) was 4:1. Control experiments (glpc analysis) established that *trans*-2-butene did not isomerize to *cis*-2-butene under the reaction conditions.

C. *cis*-2-Butene.—Analysis of the crude product by glpc indicated that the same products were formed as in the previous experiment but that in this case the ratio of the *trans*-aziridine to the *cis*-aziridine was 1:1.6. The major isomer was isolated by preparative glpc and determined to be 1-*n*-butoxy-*cis*-2,3-dimethylaziridine (**13**): ir ($CHCl_3$) 2975, 1740, 1460, 1380, 1210, 1070, and 970 cm^{-1}; nmr ($CDCl_3$) δ 3.7 (t, 2 H, J = 6 Hz) and 0.7–2.3 (m, 15 H); mass spectrum m/e 70 (base peak), 57, 56, 55, 42, 41.

Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.19; H, 12.08; N, 9.68.

The minor component was isolated by preparative glpc and determined to be **12** by comparison of its ir spectrum with that of material from the previous experiment.

Pyrolysis of Lithio Derivative of *N*-*p*-Toluenesulfonyl-*O*-diphenylmethylhydroxylamine (6a).—*n*-Butyllithium in hexane (2.6 ml, 6.1 mmol) was added to a solution of 2.00 g (5.67 mmol) of **6a** in 25 ml of triglyme and the solution was heated at 165° for 18 hr. The reaction mixture was poured into 200 ml of water and extracted with four 50-ml portions of ether and the ether extracts were washed with three 20-ml portions of water and dried ($MgSO_4$). Evaporation of the ether left the crude product, which was chromatographed on 30 g of silica gel. The column was eluted with 100 ml of hexane, 200 ml of 1:1 hexane–ether, and 100 ml of ether. All of the product was eluted in the hexane–ether mixture fraction and was identified as benzophenone oxime (1.13 g, 100%), mp 134–139° (reported mp 143–144°).[24] The ir spectrum of the product was identical with that of authentic material. Recrystallization from ethanol–water raised the melting point to 136–138°.

The aqueous layers from the extractions were combined and acidified with 12 *N* hydrochloric acid and extracted with three 50-ml portions of ether. The ether extracts were washed with 20-ml portions of water, dried over magnesium sulfate, and evaporated to leave 1.07 g of crude product which was washed well with *n*-hexane to afford 500 mg (57%) of *p*-toluenesulfinic acid, mp 83–87° (reported mp 85–90°),[24] which was identical with authentic material in its ir spectrum.

Pyrolysis of Sodio Derivative of 6a. Two Equivalents of NaH.—A solution containing 2.00 g (5.67 mmol) of **6a** and 0.546 g (11.3 mmol) of sodium hydride as a 50% dispersion in mineral oil in 25 ml of triglyme was heated at 200° for 14 hr. The reaction mixture was poured into 400 ml of water and extracted with four 50-ml portions of ether and the combined ether extracts were washed with four 25-ml portions of water. After drying ($MgSO_4$) and evaporation of the solvent, the crude product was chromatographed on 30 g of silica gel and eluted successively with 150 ml of *n*-hexane, 100 ml of 1:1 hexane–ether, and 200 ml of ether. The first fraction contained 0.13 g of mineral oil.

(24) R. C. Weast, Ed., "Handbook of Chemistry and Physics," 47th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1966.

(25) A. C. Cope and A. C. Haven, Jr., *J. Amer. Chem. Soc.*, **72**, 4896 (1950).

The second fraction contained 650 mg (58%) of benzophenone oxime identified by its ir spectrum, which was identical with that of authentic material. Recrystallization from ethanol–water gave material of mp 141–142°.

Four Equivalents of NaH.—To a solution of 353 mg (1.0 mmol) of **6a** in 10 ml of diglyme was added 172 mg (4 mmol) of a 56% sodium hydride dispersion in mineral oil and the reaction mixture was refluxed for 1 hr, during which time a large amount of solid formed. The reaction mixture was poured into 75 ml of water and extracted with three 20-ml portions of ether and the combined ether extracts were washed with three 10-ml portions of water. After drying ($MgSO_4$) and evaporation of the ether the product was heated at 100° (1 mm) to remove residual diglyme and the residue was taken up in hexane. Cooling of the hexane solution resulted in the deposit of 98.3 mg (56%) of benzhydrol, mp 62–65° (reported mp 68–69°),[24] identified by its ir spectrum, which was identical with that of authentic material.

Similar results were obtained when **6a** was heated at 200° for 22 hr with 10 equiv of sodium hydride in triglyme.

Ten Equivalents of NaD.—Sodium deuteride was added as a 50% suspension in mineral oil (1.0 g, 20 mmol) to a solution of 748 mg (2.1 mmol) of **6a** in 25 ml of triglyme and the solution was refluxed for 15 hr. Work-up afforded 245 mg (64%) of benzhydrol, mp 63–64°. The ir and nmr were identical with those of an authentic sample and showed no evidence for deuterium incorporation.

Pyrolysis of Sodio Derivative of *N*-*p*-Toluenesulfonyl-*O*-diphenylmethylhydroxylamine (7a).—A solution of **7a** (530 mg, 1.92 mmol) in 25 ml of triglyme was heated with 184 mg (3.84 mmol) of a 50% dispersion of sodium hydride in mineral oil at 200° for 14 hr. The reaction mixture was worked up as described above for **6a** and the crude product was washed with pentane to afford 180 mg (48%) of benzophenone oxime, mp 136–140°.

Reaction of *N*-Methyl-*N*-*p*-toluenesulfonyl-*O*-diphenylmethylhydroxylamine (18) with NaH.—To 1.0 g (2.7 mmol) of **18** in 50 ml of triglyme was added 5.4 mmol of sodium hydride and the solution was heated at 210° for 19 hr. The reaction mixture was quenched with 400 ml of water and worked up as in previous experiments. The crude product was purified by preparative tlc using a *n*-hexane–ether (2:1) solution to yield 66 mg (13%) of benzophenone, 281 mg (57%) of benzhydrol, mp 61–62°, and 122 mg (24%) of *N*-methyl-*p*-toluenesulfonamide, mp 65–72° (lit.[24] mp 78–79°). The ir and nmr were shown to be identical with those of authentic samples of benzophenone, benzhydrol, and *N*-methyl-*p*-toluenesulfonamide, respectively.

The base-soluble fraction was purified by preparative tlc using a *n*-hexane–ether (2:1) solution to yield 73 mg (14.7%) of benzhydrol, mp 58–63°, 10 mg (3%) of benzoic acid, and 111 mg (22%) of *N*-methyl-*p*-toluenesulfonamide. The ir and nmr were shown to be identical with those of authentic samples of benzhydrol, benzoic acid, and *N*-methyl-*p*-toluenesulfonamide, respectively.

Reaction of *N*-Methyl-*N*-*p*-toluenesulfonyl-*O*-diphenylmethylhydroxylamine-α-d_1 with NaH.—Repetition of the preceding experiment using 441 mg (1.2 mmol) of the title compound afforded a crude product which was purified by preparative tlc (2:1 hexane–ether) to yield 168 mg (65%) of unlabeled benzhydrol, mp 63–65°. The ir, nmr and mass spectra were identical with those of an authentic sample.

A control experiment in which Ph_2CDOH was heated at 135° for 18 hr in triglyme resulted in a 71% recovery of benzhydrol which retained 90% of the original deuterium (nmr analysis).

Attempted Reaction of Benzophenone with *p*-Toluenesulfonamide.—*p*-Toluenesulfonamide (970 mg, 5.67 mmol) was dissolved in dry triglyme (25 ml). A 50% oil dispersion of sodium hydride (545 mg, 10.4 mmol) was added slowly and the reaction was stirred for 15 min. Benzophenone (1.0 g, 5.67 mmol) was added and the reaction was heated at 185° for 19 hr. Work-up was carried out as described in previous experiments. The crude product weighed 1.13 g. A portion of this product (405 mg) was separated by preparative tlc using 2:1 hexane–ether as the developing solvent to yield 125 mg of benzophenone and 114 mg of benzhydrol, mp 64–65°. These amounts correspond to yields of 36 and 32%, respectively. The identity of the products was established by comparison of their ir spectra with those of authentic material.

Reactions of *N*-*p*-Toluenesulfonyl-*O*-benzylhydroxylamine with Sodium Hydride. A.—To 2.0 g (7.2 mmol) of **6b** in 200 ml of purified tetrahydrofuran was added 1 equiv of sodium hydride. The reaction mixture was stirred for 30 min and the solvent was evaporated under reduced pressure. The salt was then heated at 192° in 100 ml of triglyme for 18 hr under nitrogen. The reaction mixture was poured into 400 ml of water and extracted with five 50-ml portions of ether. The ether extracts were then washed with three 50-ml portions of water and dried over magnesium sulfate. The residue after evaporation of the ether was chromatographed on 50 g of silica gel and eluted successively with 100 ml of hexane, 200 ml of 3:1 hexane–ether, and 200 ml of 1:1 hexane–ether. The middle fractions on evaporation afforded 263 mg (35%) of benzonitrile, which was identified by comparison of its ir spectrum and glpc retention time with those of authentic material. Further elution with ether removed 162 mg (8%) of *N*-*p*-toluenesulfonylbenzylamine, mp 108–112° (reported[26] mp 116°), which was identical with an authentic sample prepared from benzylamine and *p*-toluenesulfonyl chloride (mp 110–112°).

B.—In another experiment 1.27 g (4.6 mmol) of **6b** was treated with 2 equiv of sodium hydride in 75 ml of triglyme at 100° for 18 hr. After work-up as described above, no product was found in the ether extracts, so the aqueous phase was acidified with 2 *N* HCl and extracted with ether (4 × 50 ml). These ether extracts were washed with two 20-ml portions of water, dried ($MgSO_4$), and evaporated and the residue was chromatographed on 30 g of silica gel. Elution with 100 ml of 1:1 ether–hexane afforded 170 mg (30%) of impure benzoic acid (mp 92–105°) the ir of which was identical with that of an authentic sample. Further elution with ether yielded 710 mg (91%) of *p*-toluenesulfonamide.

Reaction of *N*-*p*-Toluenesulfonyl-*O*-*p*-bromobenzylhydroxylamine with Sodium Hydride.—Two equivalents of sodium hydride was added to a solution of 2.0 g (5.6 mmol) of **6c** in 50 ml of triglyme and heated at 200° for 21 hr. The reaction mixture was worked up as described for the reactions of **6b**. No identifiable products could be obtained from the neutral fraction.

The base-soluble fraction was chromatographed on silica gel and eluted with chloroform (3 × 50 ml), a *n*-hexane–ether (1:1) solution (4 × 50 ml), and finally ether (100 ml). Fractions 1, 3, 4, and 6 yielded 71 mg of unidentifiable products. Fractions 2 and 5 yielded 480 mg (41%) of *p*-bromobenzoic acid, mp 235–240° (lit. mp 254.4°).[24] Fractions 7 and 8 yielded 350 mg (36%) of *p*-toluenesulfonamide, mp 134–136° (lit. mp 137.5°).[24] The products were shown to be identical with authentic samples of *p*-bromobenzoic acid and *p*-toluenesulfonamide, respectively, by ir and mixture melting point.

Reaction of *N*-*p*-Toluenesulfonyl-*O*-*p*-methoxybenzylhydroxylamine with Sodium Hydride.—The title compound **6d** (1.0 g, 3.26 mmol) was dissolved in 100 ml of tetrahydrofuran and treated with 3 equiv of sodium hydride, and the reaction mixture was stirred for 30 min. The solvent was evaporated under reduced pressure. The salt was heated in 50 ml of triglyme at 150–160° for 18 hr under a nitrogen atmosphere. The reaction was worked up according to the procedure described previously. No product was obtained from the base-insoluble fraction.

The base-soluble fraction was eluted with chloroform (100 ml) and a *n*-hexane–ether (1:1) solution (100 ml) to yield 94 mg of unidentifiable products. Elution with more *n*-hexane–ether (1:1) solution (100 ml) yielded 195 mg (39%) of *p*-methoxybenzoic acid, mp 176–181° (lit. mp 185°).[24] Elution with ether (100 ml) yielded 150 mg (27%) of *p*-toluenesulfonamide, mp 121–123° (lit. mp 137.5°).[24] The ir and nmr were shown to be identical with those of authentic samples of *p*-methoxybenzoic acid and *p*-toluenesulfonamide, respectively.

Reaction of Benzaldehyde with *p*-Toluenesulfonamide in the Presence of NaH.—*p*-Toluenesulfonamide (1.0 g, 5.85 mmol) was dissolved in dry triglyme (25 ml) and treated with 2 equiv of a 50% oil dispersion of sodium hydride, and the reaction mixture was stirred for 15 min. Benzaldehyde (620 mg, 5.85 mmol) was added and the reaction was heated at 205° for 18 hr under a nitrogen atmosphere. Work-up was accomplished as described in the preceding experiments and the crude mixture of products was separated by preparative tlc using chloroform to yield 172 mg (11%) of *N*-*p*-toluenesulfonylbenzylamine, mp 107–109°, and 93 mg (15%) of benzyl alcohol shown by ir and nmr to be identical with authentic samples.

The base-soluble fraction was purified by preparative tlc using a *n*-hexane–ether (2:1) solution to yield 340 mg (48%) of benzoic

(26) "Handbook of Tables for Organic Compound Identification," 3rd ed, Z. Rappaport, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1967.

acid and 550 mg (55%) of *p*-toluenesulfonamide. The ir were shown to be identical with that of authentic samples.

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Registry No.—**5a**, 1782-38-3; **5b**, 1944-96-3; **5d**, 5622-7-5; **6a** lithio derivative, 40780-47-0; **6a** sodio derivative, 40780-48-1; **6b**, 1576-39-2; **6c**, 40780-50-5; **6d**, 40780-51-6; **7a** sodio derivative, 40780-52-7; **9**, 30542-59-7; **11**, 40780-54-9; **12**, 40780-55-0; **13**, 40780-56-1; **18**, 30646-06-1; **18** α-d_1 derivative, 40780-58-3; nickel peroxide, 1313-99-1; *N*-bromosuccinimide, 128-08-5; lead tetraacetate, 546-67-8; tetramethylethylene, 563-79-1; *trans*-2-butene, 624-64-6; *cis*-2-butene, 590-18-1; sodium hydride, 7646-69-7; benzophenone, 119-61-9; *p*-toluenesulfonamide, 70-55-3; benzaldehyde, 100-52-7; *O*-*p*-bromobenzylhydroxylamine hydrochloride, 40780-59-4; *O*-*p*-methoxybenzylhydroxylamine hydrochloride, 876-33-5; benzhydrol-d_1, 17498-07-6; bromodiphenylmethane-d_1, 40780-62-9.

Supplementary Material Available.—A description of the instruments used and details of the syntheses, spectral and physical properties, and microanalytical combustion data of the starting materials will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3107.

The Effect of Added Electron Acceptor on the Methylene–Azomethine Rearrangement, a Trapped Transamination

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It has been shown that the carbanion intermediate in the hydrogen–deuterium exchange of *N*-neopentylidenebenzylamine, IV, can be intercepted by nitrobenzene and in the presence of oxygen converted to benzoic acid, pivalic acid, benzamide, and pivalamide. A detailed kinetic analysis of exchange, isomerization, and trapping processes has been carried out. Evidence that this reaction occurs for other azaallylic anions is also presented.

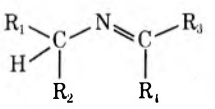
For many years, the methylene–azomethine rearrangement was thought to occur *via* a one-step mechanism involving a single transition state.[1] More recently it has been shown that the reaction actually involves a carbanion intermediate.[2] Although the evidence presented for this mechanistic revision has met with some skepticism,[3] the number of examples of imine systems for which one of the tautomers undergoes base-catalyzed hydrogen–deuterium exchange faster than isomerization has grown to the point where there can be little doubt as to the generality of the carbanion mechanism.[4]

Our recent success in the application of electron-transfer trapping to the elucidation of the mechanistic details of carbanion reactions[5] prompted us to apply the technique to the base-catalyzed methylene–azomethine rearrangement. We did this not so much to demonstrate the intermediacy of carbanions, a point which we feel has been adequately documented, but rather to extend the technique to a new kind of carbanion intermediate, to examine the kinetic problems of dealing with isomerizing systems by this method, and hopefully to find ways in which the technique can be applied to cases for which electron-transfer trapping can be coupled with the subtleties of stereochemistry in such reactions. We hope in this way to learn more about both the methylene–azomethine rearrangement and the process of electron transfer. We report here our preliminary efforts.

Results

The major remaining problem to application of the electron transfer trapping technique to the entire spectrum of carbanion reactions is the requirement that the acceptor be stable to the reaction conditions. In reactions where carbanions are generated by proton removal this means that the acceptor must not react with the base. Nitroaromatics work well but have limitations. As regards alkoxide bases, primary and secondary alkoxides will reduce aromatic nitro compounds to azoxy compounds in the vicinity of 70°.[6] Potassium *tert*-butoxide, a stronger base, will not react appreciably at 50°.

In the general formulation shown the R groups must then be selected such that the ionization can be carried



out either below 70° in methoxide–methanol or ethoxide–ethanol or between 20° and 50° in potassium *tert*-butoxide–*tert*-butyl alcohol. When $R_1 = R_3$ = aryl and $R_2 = R_4 = H$, isomerization can be effected at 80° in ethanol–ethoxide.[7]

When *N*-benzylidenebenzylamine (I) was allowed to react with nitrobenzene and 0.6 *N* potassium *tert*-butoxide in *tert*-butyl alcohol at 30°, the imine was destroyed within 20 min and a precipitate of potassium

(1) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 1st ed, Cornell University Press, Ithaca, N. Y., 1953, p 572.

(2) (a) D. J. Cram and R. D. Guthrie, *J. Amer. Chem. Soc.*, **87**, 397 (1965); (b) D. J. Cram and R. D. Guthrie, *ibid.*, **88**, 5760 (1966).

(3) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 837.

(4) (a) R. D. Guthrie, W. Meister, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 5288 (1967); (b) R. D. Guthrie, D. A. Jaeger, W. Meister, and D. J. Cram, *ibid.*, **93**, 5137 (1971); (c) D. A. Jaeger and D. J. Cram, *ibid.*, **93**, 5153 (1971).

(5) (a) R. D. Guthrie, *J. Amer. Chem. Soc.*, **91**, 6201 (1969); (b) R. D. Guthrie, *ibid.*, **92**, 7219 (1970); (c) R. D. Guthrie, A. T. Young, and G. W. Pendygraft, *ibid.*, **93**, 4947 (1971); (d) R. D. Guthrie, *Intra-Sci. Chem. Rep.*, in press.

(6) Y. Ogata and J. Mibae, *J. Org. Chem.*, **27**, 2048 (1962).

(7) C. W. Shoppee, *J. Chem. Soc.*, 1225 (1931); (b) E. De Salas and C. H. Wilson, *ibid.*, 319 (1938).

nitrobenzenide[8] was observed. Compound I was stable to these conditions in the absence of nitrobenzene.

When the less acidic *N*-benzylidene-α-phenylethylamine (II) was subjected to the conditions described for I, II disappeared from the reaction mixture at a rate comparable to the rate at which it isomerizes to *N*-(α-methylbenzylidene)benzylamine (III) in the absence of nitrobenzene (half-life of roughly 50 min). When III was subjected to these conditions, it was no longer detectable by gas chromatography after 16 min. It appeared, therefore, that III was also too acidic and that, although II was not, there was no way to tell whether II was destroyed on the way to III or after it arrived. This analysis was supported by the observation that III underwent rapid hydrogen–deuterium exchange of both its methyl and methylene hydrogens with nitrobenzene absent.

If an excess of III (0.211 *M*) and nitrobenzene (0.32 *M*) was employed in 0.05 *N* potassium *tert*-butoxide in *tert*-butyl alcohol, the reaction stopped after 33% loss of III (very little change between 15 or 30 min) and very little deuterium was incorporated in unreacted III. This suggested that electron transfer from the carbanion was faster than reprotonation but because ionization was too rapid for convenient kinetic analysis we pursued the study of this system no further.

Finally, we prepared *N*-neopentylidenebenzylamine (IV), which at 50° in potassium *tert*-butoxide–*tert*-butyl alcohol underwent isomerization to *N*-benzylideneneopentylamine (V), hydrogen–deuterium exchange, and reaction with nitroaromatics at measurable rates. For convenience, the reaction was carried out in the presence of oxygen, which regenerated nitrobenzene and simplified the products. No direct reaction of the substrate with oxygen was observed under the reaction conditions in the absence of nitrobenzene. The initial rate of substrate loss appeared to be slightly higher in the presence of oxygen, although the experimental error is quite large for initial rate determinations because the species being measured is the starting reagent rather than the products.

The products of the reaction carried out in an oxygen atmosphere were benzamide, pivalamide, benzoic acid, and pivalic acid. No significant amounts of benzaldehyde or pivalaldehyde could be detected. When the reaction was carried out under anaerobic conditions nitrobenzene was lost as the reaction proceeded. Roughly 1.5–2 mol of nitrobenzene disappeared for every mole of substrate lost and the appearance of azoxybenzene was observed.

For purposes of comparison with electron transfer trapping runs, isomerization and exchange of IV was carried out in the absence of nitrobenzene. The concentrations of all species are obtainable by combining mass spectral and gas chromatographic analyses. The data could be analyzed in terms of Scheme I.

The analysis was carried out as follows. (1) k_5 was determined by studying the isomerization of IV-d_2 under the conditions described for run 1. This run (run 2) gave good pseudo-first-order kinetics with $k_5 = 0.765 \pm 0.008 \times 10^{-6}$ sec^{-1},[9] through 30% isomerization. (2) Compound V-h_2 was found to undergo no measurable exchange or isomerization under the conditions of runs 1 and 2 and therefore the formation of V was assumed to be irreversible. (3) Integrated rate equations were obtained for Scheme I. (4) The relationship $k_4 = (k_5k_2/4k_3) + (k_1k_3/k_2)$ was assumed. (5) A unique set of rate constants were obtained as listed in Table I.

(8) G. A. Russell and A. G. Bemis, *Inorg. Chem.*, **6**, 403 (1967).
(9) Error limits given represent one standard deviation.

SCHEME I

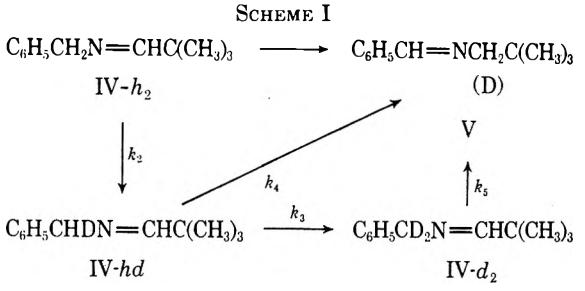


TABLE I

RATE CONSTANTS FOR EXCHANGE AND ISOMERIZATION OF IV-h_2 IN *tert*-BUTYL ALCOHOL-*O*-*d*–POTASSIUM *tert*-BUTOXIDE (0.592 *N*) AT 50° (RUNS 1 AND 2)

Rate constant or ratio	Value × 10^6, sec^{-1}	Significance
k_1	0.292	Isomerization of IV-h_2
k_2	6.93	Exchange of IV-h_2
k_3	2.87	Exchange of IV-*hd*
k_4	0.168	Isomerization of IV-*hd*
k_5	0.0765	Isomerization of IV-d_2
k_2/k_1	24	Collapse ratio
$k_2/2k_3$	1.21	Secondary isotope effect (k_H/k_D)
k_1/k_5	3.81	Primary isotope effect on isomerization (k_H/k_D)

Table II gives a comparison of the measured concentrations and those calculated using the rate constants of Table I.

TABLE II

EXCHANGE AND ISOMERIZATION OF *N*-NEOPENTYLIDENEBENZYLAMINE (IV-h_2) IN *tert*-BUTYL ALCOHOL-*O*-*d* CATALYZED BY POTASSIUM *tert*-BUTOXIDE (0.592 *N*) AT 50.0° (RUN 1)

Time, sec (× 10^4)	% IV-h_2		% IV-*hd*		% IV-d_2		% V	
	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd
0.486	70.3	70.4	27.2	26.3	1.1	2.0	1.3	1.3
0.852	52.7	54.0	39.7	38.3	5.5	5.4	2.3	2.2
1.458	34.3	34.9	48.9	48.6	13.4	13.1	3.5	3.5
2.916	12.5	12.2	47.5	48.2	33.8	33.8	6.1	5.9
4.116	5.9	5.1	39.4	39.0	47.5	48.4	7.1	7.4

The exchange and isomerization of IV-d_2 in *tert*-butyl alcohol-*O*-*h* was also studied and analogous rate constants were obtained by the same method of calculation. The results are displayed in Table III. The determination of k'_1 is inherently inaccurate because the bulk of isomerization comes *via* exchanged starting material.

Having satisfactorily analyzed this system of four intermediates, we then considered the additional complications arising with an electron acceptor present in the reaction mixture. Under these circumstances the kinetic situation is represented by Scheme II. This system was treated as follows. (1) The loss of IV-h_2 in *tert*-butyl alcohol-*O*-*h* was studied and the results were fitted by numerical integration. Best results

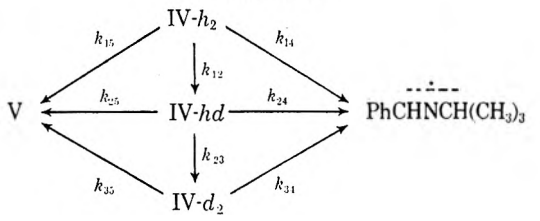
TABLE III

RATE CONSTANTS FOR EXCHANGE AND ISOMERIZATION OF IV-d_2[a] IN *tert*-BUTYL ALCOHOL–POTASSIUM *tert*-BUTOXIDE (0.628 *N*) AT 50° (RUNS 3 AND 4[b])

Rate constants and ratios	Values × 10^6, sec^{-1}	Significance
k'_1	0.0483	Isomerization of IV-d_2
k'_2	2.01	Exchange of IV-d_2
k'_3	1.25	Exchange of IV-*hd*
k'_4	0.101	Isomerization of IV-*hd*
k'_5[b]	0.176	Isomerization of IV-d_2
k'_5/k'_1	3.65	Primary isotope effect on isomerization (k_H/k_D)
$k'_3/2k'_2$	1.23	Secondary isotope effect on isomerization (k_H/k_D)
k'_2/k'_1	41.5	Collapse ratio

[a] The starting material contained 3.3% of material having only one deuterium atom. [b] The value of k'_5 was determined separately by studying isomerization of IV-h_2 in *tert*-butyl alcohol-*O*-*h*. This is referred to as run 4.

SCHEME II



were obtained by assuming a stoichiometry of 2.5 mol of base loss per mole of substrate loss. This value was used in subsequent calculations. (2) Isomerization and loss of IV-d_2 in *tert*-butyl alcohol-*O*-*d* was studied and the results, which yielded values of k_{34} and k_{35}, are given in Table IV. (3) It was assumed that $k_{35}k_4/k_5 =$

TABLE IV

ISOMERIZATION AND LOSS OF *N*-NEOPENTYLIDENE-α-DIDEUTERIOBENZYLAMINE (IV-d_2)[a] WITH 0.592 *N* POTASSIUM *tert*-BUTOXIDE AND 0.206 *M* NITROBENZENE IN *tert*-BUTYL ALCOHOL-*O*-*d* AT 50° (RUN 6)

Time × 10^{-4}, sec	V, % Found	V, % Calcd[c]	Loss,[b] % Found	Loss,[b] % Calcd[c]
2.760	1.2	1.4	27.4	28.5
6.510	2.6	2.6	47.8	47.4
11.47	3.8	3.5	62.9	64.1
16.53	4.2	4.0	74.0	74.1
28.53	5.2	4.7	84.9	85.8

[a] Contained 3.3% of IV-*hd*. [b] By gas chromatographic comparison with bicyclohexyl as an internal standard. [c] Calculated using initial first-order rate constants: $k_{34} = 1.16 \times 10^{-5}$ and $k_{35} = 0.63 \times 10^{-6}$ sec^{-1} by numerical integration assuming loss of 2.5 mol of base/mol of substrate.

k_{25} and that $k_{24} = (k_{14}k_{23}/k_{12}) + (k_{34}k_{12}/4k_{23})$. (4) Numerical integration was carried out making minor adjustments for dilution of the deuterium pool and the rate constants were adjusted iteratively to fit the data of run 7 which is given in Table V. A unique set of rate constants was obtained as given in Table VI. (5) The analogous procedure was carried out for the reaction of IV-d_2 and the results are given in Tables VII and VIII.

Finally, several runs were carried out using IV-h_2 in *tert*-butyl alcohol-*O*-*h* at different nitrobenzene concentrations and two runs were made with *p*-chloronitrobenzene as acceptor. These are listed in Table IX.

Discussion

It is well accepted that a variety of carbon acids will react with nitroaromatics *via* electron transfer from a carbanion intermediate as detailed in Scheme III.[10]

SCHEME III

$$RH + B^- \longrightarrow R^-$$

$$R^- + ArNO_2 \longrightarrow R\cdot + ArNO\cdot_2^-$$

The carbanion intermediate in the methylene–azomethine rearrangement seems unexceptional in this regard, as we have now demonstrated characteristic behavior for several such systems. The compound studied in greatest detail, IV, behaved in a manner analogous to that observed by Russell for the nitrobenzene-catalyzed reaction of fluorene with oxygen to give fluorenone,[11] with the exception that oxidation was more extensive in our system.

The collapse ratio for the carbanion from IV favors protonation to give IV rather than V by a large factor. This system is therefore behaving more like a charge-localized rather than an ambident anion. We hope to find systems which depart from this simple behavior for future study. The collapse ratio for this system is much larger when the exchange of deuterated substrate is considered (see Tables I and III). Curiously, this is opposite to a previously studied system.[4b]

When nitrobenzene is added to the isomerizing and exchanging mixture of IV and base, the kinetic situation becomes quite complex; however, a number of interesting qualitative and semiquantitative conclusions can be drawn.

It is significant that the isotope effect on loss of IV in run 7 is roughly a factor of 2 lower than that for isomerization (see Table VI). Because most of the loss of IV occurs directly from unexchanged IV-h_2 and Table V shows agreement of calculated and experimental values within normal gas chromatographic reproducibility, the value of k_{14} should be accurate to within a few per cent, as should k_{14}/k_{34}. If the amount of isomerized product represents a constant fraction of the anions formed (independent of the origin of the anion), then the amount of material oxidized must not. The results could be explained if a lower fraction of the anions arising from IV-h_2 gave electron transfer than those arising from IV-d_2. Clearly this demonstrates that the anions arising from protio and deuterio substrate are different and this difference is explicable in terms of specific solvation by the alcohol molecule generated by base attack. When the alcohol molecule is *tert*-butyl alcohol-*O*-*h*, internal return is favored by the kinetic isotope effect and electron transfer trapping is less efficient.

Data obtained using IV-d_2 as substrate in *tert*-butyl alcohol-*O*-*h* is also included for completeness, although, as previously mentioned, the inaccuracies are magnified in this case by the preference for reaction *via* exchanged IV. The significant features of this data (listed in Table VIII) are the similarity of the value determined for the kinetic isotope effect on loss to that

(10) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Amer. Chem. Soc.*, **86**, 1807 (1964).

(11) G. A. Russell, A. G. Bemis, E. J. Geels, E. G. Janzen, and A. J. Moye, *Advan. Chem. Ser.*, **75**, 174 (1968).

TABLE V

CALCULATED AND OBSERVED PRODUCT DISTRIBUTION IN THE REACTION OF *N*-NEOPENTYLIDENEBENZYLAMINE (0.101 *M*) WITH NITROBENZENE (0.206 *M*) AND POTASSIUM *tert*-BUTOXIDE (0.592 *N*) IN *tert*-BUTYL ALCOHOL-*O*-*d* AT 50° IN OXYGEN ATMOSPHERE (RUN 7)

Time × 10^{-4},	IV-h_2, %		IV-hd, %		IV-d_2, %		V, %		Loss, %	
sec^{-1}	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd
0.7620	54.0	53.7	26.2	27.2	2.7	2.9	1.6	1.8	15.6	14.5
1.596	29.5	29.6	34.3	34.2	8.0	8.0	3.1	3.0	25.1	25.2
2.5560	16.1	16.0	33.3	32.9	13.1	13.1	4.1	3.9	33.1	34.1
3.210	10.7	10.9	30.7	30.1	16.6	15.8	4.6	4.4	37.3	38.8
7.872	1.7	1.3	11.9	12.5	22.6	21.4	6.1	6.1	57.7	58.7

TABLE VI

RATE CONSTANTS USED FOR CALCULATING PRODUCT DISTRIBUTION IN RUN 7 (TABLE V)

Rate constant or ratio	Value × 10^5, sec^{-1}	Significance
k_{12}	6.07	Exchange of IV-h_2
k_{14}	2.34	Loss of IV-h_2
k_{15}	0.29	Isomerization of IV-h_2
k_{23}	2.75	Exchange of IV-hd
k_{24}	1.70	Loss of IV-hd
k_{25}	0.166	Isomerization of IV-hd
k_{34}	1.16	Loss of IV-d_2
k_{35}	0.0631	Isomerization of IV-d_2
k_{15}/k_{35}	4.6	Primary isotope effect on isomerization (k_H/k_D)
k_{14}/k_{34}	2.02	Primary isotope effect on loss (k_H/k_D)
$k_{12}/2k_{23}$	1.10	Secondary isotope effect on exchange (k_H/k_D)
k_{12}/k_{15}	21	Collapse ratio
k_{14}/k_{12}	0.386	Trapping efficiency (k_e/k_d)

discussed above and the lower trapping efficiency in this protic solvent. When the trapping efficiency in deuterated solvent (k_e/k_d) is divided by that for protio solvent (k_e/k_h) the resultant value $k_h/k_d = 2.1$ is the effective isotope effect on reprotonation of the carbanion intermediate. This type of calculation has been discussed previously[5b] and assumes that only protonation and not electron transfer rates are affected by the isotopic nature of the solvent medium. In the example previously studied,[5b] it was found that the isotope effect on carbanion reprotonation was very similar to the primary isotope effect on ionization. The fact that the difference between reprotonation rates in the isotopically different solvents is smaller than the ionization isotope effect in this case is probably another indication of the involvement of intramolecularity.

Still another indication that intramolecular reprotonation is occurring is the observation that the total $k_{12} + k_{14} + k_{15}$ (see Table VI) is greater than the total $k_1 + k_2$ (see Table I). As these sums represent the total observable processes undergone by the carbanion in each case, it is clear that we have observed a greater fraction of the total carbanions with nitrobenzene present. This is also true starting from IV-d_2, but we have previously qualified our faith in the rate constants obtained with this starting material and the fact that k'_{12} is slightly greater than k'_2 makes us suspicious that the value measured for k'_{12} is somewhat high.

Our failure to find an acceptor which would trap the anion from IV at the ionization limit is a final interesting feature of this system.[5b] The data given in Table IX shows that the loss of IV from the reaction mixture is reasonably close to first order in both nitrobenzene and potassium *tert*-butoxide, as would be expected. The unexpected feature of this data is that substitution of *p*-chloronitrobenzene had such a minor effect on the rate of loss. By contrast, in the case of 9-methoxyfluorenide ion, *p*-chloronitrobenzene increases the trapping efficiency by a factor of 7.[12] There are several mechanistic schemes which could explain the insensitivity to acceptor nature in this system. A trivial situation would be that in which all carbanions formed were trapped, the process of loss becoming ionization limited. This is clearly not the case, as indicated by the trapping efficiency in Table VIII. A modification would arise if two types of intermediate were involved, only one of which was being trapped by nitroaromatics. This would result in an upper limit of k_{loss}. It is clear that this explanation cannot account for the fact that the reaction is approximately first order in nitrobenzene.

It seems most likely that we have found a case in which the rate of loss of substrate is limited to some degree by the rate of encounter of the carbanion and the nitroaromatic. The fact that the rate constant for loss is increased slightly by the change from nitrobenzene to *p*-chloronitrobenzene suggests that encounter is reversible to some small extent. The encounter rate could be limited either by diffusion of the carbanion and nitroaromatic together in solution or by the breaking of a solvation sheath by the nitroaromatic prior to complex formation and subsequent electron transfer.

Experimental Section

Solvent and Solutions.—*tert*-Butyl alcohol was purified by distillation from molecular sieves (type 3A) on to molecular sieves. For some reactions further purification was carried out by treating 2.5 kg of the alcohol with 21.4 g of potassium. When the potassium had reacted, 100 ml of nitrobenzene was added and the mixture was stirred at 50° in oxygen for 72 hr. The alcohol was separated by distillation and purified by distilling from calcium oxide after 24 hr reflux. The final distillation was carried out from molecular sieves onto molecular sieves through a 2-ft Widmer column. This latter procedure is recommended for future work as it eliminated a side reaction between an unidentified impurity in the *tert*-butyl alcohol and nitrobenzene.

Solutions of potassium *tert*-butoxide in *tert*-butyl alcohol were prepared by dissolving potassium metal in the alcohol under oxygen-free nitrogen. *tert*-Butyl alcohol-*O*-*d* was prepared by a published procedure[13] and contained 98–99% of one atom of deuterium by nmr.

Nitrobenzene was purified as previously described.[14]

***N*-Benzylidenebenzylamine** (I) was prepared by a published procedure.[15] Its nmr spectrum agreed with that predicted.

(12) R. D. Guthrie and G. W. Pendygraft, unpublished results.

(13) A. T. Young and R. D. Guthrie, *J. Org. Chem.*, **35**, 853 (1970).

(14) R. D. Guthrie and D. W. Wesley, *J. Amer. Chem. Soc.*, **92**, 4057 (1970).

(15) R. Perez-Ossorio, J. M. Gamboa, and R. M. Utrilla, *An. Real Soc. Espan. Fis. Quim., Ser. B*, **53**, 17 (1956).

TABLE VII

CALCULATED AND OBSERVED PRODUCT DISTRIBUTION IN THE REACTION OF *N*-NEOPENTYLIDENEBENZYLAMINE-α-d_2 (0.102 *M*) WITH NITROBENZENE (0.205 *M*) AND POTASSIUM *tert*-BUTOXIDE (0.628 *N*) IN *tert*-BUTYL ALCOHOL (RUN 8)

Time,	IV-d_2, %		IV-*hd*, %		IV-h_2, %		V, %		Loss, %	
× 10^4, sec	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd	Found	Calcd
0.7440	78.8	79.4	15.3	15.9	1.3	1.0	0.7	0.6	3.8	3.0
1.476	64.8	65.3	22.9	24.3	2.6	3.1	1.3	1.1	8.4	6.2
3.198	43.3	42.4	33.3	32.6	8.2	9.0	2.6	2.5	12.6	13.5
9.618	9.6	9.9	24.4	23.2	21.9	22.2	5.6	7.0	38.6	37.8
20.44	1.34	1.31	7.36	7.12	20.1	18.2	10.7	11.4	60.5	62.0

TABLE VIII

RATE CONSTANTS USED FOR CALCULATING PRODUCT DISTRIBUTION IN RUN 8 (TABLE VII)

Rate constant or ratio	Value × 10^6, sec^{-1}	Significance
k'_{12}	2.21	Exchange of IV-d_2
k'_{14}	0.397	Loss of IV-d_2
k'_{15}	0.0739	Isomerization of IV-d_2
k'_{23}	1.51	Exchange of IV-*hd*
k'_{24}	0.619	Loss of IV-*hd*
k'_{25}	0.115	Isomerization of IV-*hd*
k'_{34}[a]	0.951	Loss of IV-h_2
k'_{35}[a]	0.177	Isomerization of IV-h_2
k'_{35}/k'_{15}	2.40	Primary isotope effect on isomerization
k'_{34}/k'_{14}	2.40	Primary isotope effect on loss
$2k'_{23}/k'_{12}$	1.37	Secondary isotope effect on exchange
k'_{12}/k'_{15}	30	Collapse ratio
k'_{14}/k'_{12}	0.180	Trapping efficiency (k_e/k_h)

[a] Taken from run designated run 9.

TABLE IX

EFFECT OF NITROAROMATIC CONCENTRATION AND NATURE ON RATE OF LOSS OF IV-h_2 IN POTASSIUM *tert*-BUTOXIDE-*tert*-BUTYL ALCOHOL AT 50° IN OXYGEN ATMOSPHERE

Run no.[d]	[KO-*t*-Bu]	[$ArNO_2$][a]	k_{loss} × 10^5, sec^{-1}	k_{loss}[b] × 10^6, M^{-2} sec^{-1}
5	0.245	0.215	0.36	0.68
10	0.509	0.126	0.57	0.89
11	0.509	0.127	0.57	0.88
9	0.628	0.206	0.95	0.73
12	0.509	0.255	1.00	0.77
13	0.509	0.385	1.49	0.76
14 and 15[c]	0.509	0.193	1.08	1.10

[a] Nitrobenzene was used except for last entry. [b] Third-order rate constant. [c] *p*-Chloronitrobenzene was used. [d] At least five points for each run.

***N*-Benzylidene-α-phenylethylamine** (II) was prepared by a published procedure.[16] Its nmr spectrum agreed with that predicted.

***N*-(α-Methylbenzylidene)benzylamine** (III) was prepared by treatment of a mixture of acetophenone (24.2 g, 0.200 mol) and benzylamine (21.4 g, 0.200 mol) with 100 ml of benzene and a catalyst prepared as follows. Benzylamine (0.5 ml) was added to a mixture of 4 g of saturated aqueous zinc chloride and 2 ml of ethanol. The white precipitate was filtered with suction and washed with 95% ethanol.

The mixture described was refluxed past a Dean-Stark trap for 12 hr. The benzene solution was filtered through Celite and the benzene was removed by rotary evaporation to give an oil. White crystals were obtained from pentane, 27.3 g, 65%. Two recrystallizations from pentane gave material of mp 44–46°. Distillation to a cold finger gave an analytical sample. *Anal.* Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.23; N, 6.691. Found: C, 85.86; H, 7.28; N, 6.74.

(16) R. Perez-Ossorio and F. G. Herrera, *An. Real Soc. Espan. Fis. Quim., Ser. B*, **50**, 875 (1954).

Preparation of *N*-Neopentylidenebenzylamine (IV-h_2).—Pivalaldehyde (18.8 g, 0.218 mol) was cooled to 0° in a flask protected by an Ascarite tube. Benzylamine (25 ml, 23.5 g, 0.220 mol) was then added dropwise with stirring over 20 min. The reaction mixture was allowed to warm to room temperature and stirred for 3 hr. Pentane (50 ml) was added and the water was separated. The pentane layer was washed with two 20-ml portions of water and dried over anhydrous sodium sulfate. Evaporation of the pentane and distillation gave 32.4 g (85%) of product: bp 123–125° (28 mm); $n^{24}D$ 1.4960; nmr (CCl_4) δ 7.58 (t, 1, neopentylidene), 7.24 (s, 5 H, phenyl), 4.52 (d, 2 H, benzyl), 1.00 (s, 9, *tert*-butyl). The ir spectrum showed a peak at 1666 cm^{-1} (C=N). An analytical sample was purified by gas chromatography. *Anal.* Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.54; H, 9.88; N, 7.77.

Preparation of Benzylamine-α-d_2.—Lithium aluminum deuteride (1.00 g, 23.8 mmol) was slurried in 30 ml of dry ether, and benzonitrile (1.8 g, 17.5 mmol) in 10 ml of ether was added dropwise with stirring over 30 min. The reaction mixture was stirred for 2 hr, treated with 15 drops of saturated aqueous Na_2SO_4, and allowed to stir for an additional 18 hr. Additional saturated Na_2SO_4 solution was added and when no heat was evolved, the reaction mixture was vacuum filtered through a Celite pad with ether washing. The ether solution was extracted with 15 ml of 10% HCl and 3 ml of water. The combined aqueous extracts were washed with 20 ml of ether and made basic with solid KOH. The resultant mixture was extracted with 30- and 20-ml portions of ether, and the ether extracts were washed with saturated aqueous NaCl and dried over anhydrous Na_2SO_4. Evaporation of the ether gave 1.50 g, which was reduced to 1.23 g (65%) after two short-path distillations. Gc analysis showed this to be mainly benzylamine with *ca.* 1% of long retention time 420 impurity.

Preparation of *N*-Neopentylidenebenzylamine-α-d_2 (IV-d_2).—The benzylamine-α-d_2 described above (1.23 g, 11.5 mol) was added to pivalaldehyde (1.00 g, 11.6 mol) as described for the preparation of IV-h_2. The product weighed 1.63 g (81%) after two short-path distillations. Mass spectral analysis at 70 eV showed a parent peak at 177 amu. The P − 1 peak was reduced to 3.3% of the ^{13}C corrected parent (about 50% of its original height) by running the spectrum at low voltage.

Preparation of *N*-Benzylideneneopentylamine (V).—Neopentylamine (2.5 g, 35 mmol) was added to benzaldehyde (3.6 g, 34 mmol) in the manner prescribed above for the preparation of IV. The same work-up procedure gave 725 mg (12%) of V, $n^{24.6}D$ 1.5096 after gas chromatographic separation from unreacted benzaldehyde. The reason for the low yield was uncertain. Mass spectral analysis at 70 eV showed a parent peak at 175 amu and a peak at P − 1, P − 1/P = 0.67. Nmr (CCl_4) showed δ 8.15 (t, 1, benzylidene), 7.2–7.8 (2 m, 5, phenyl), 3.30 (d, 2 H, neopentyl), 0.98 (s, 9, *tert*-butyl). Ir showed C=N at 1643 cm^{-1}. *Anal.* Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.13; H, 9.61; N, 7.72.

Kinetic Runs.—A mixture of substrate, nitrobenzene, and bicyclohexyl was added to a temperature-equilibrated, oxygen-filled reaction vessel containing the solvent and base (10 ml) through a rubber septum using a calibrated syringe. Aliquots (2 ml) were withdrawn at timed intervals (with addition of oxygen) and added to a mixture of 25 ml of pentane and 40 ml of ice–water. The pentane layer was washed with 20- and 10-ml portions of ice–water and dried over anhydrous sodium sulfate. The pentane solution was concentrated by rotary evaporation and kept cold when concentrated. Analysis was carried out on a 15–20-ft column of either SE-30 or SF-96 silicone grease (20% on Chromosorb W) at 200°. Where deuterium analysis was required, the substrate was collected from the gas chromatograph

and analyzed on an Hitachi Model RMU 6-E double-focusing mass spectrometer at low voltage.

Isolation of Potassium Nitrobenzenide from the Reaction of *N*-Benzylidenebenzylamine with Potassium *tert*-Butoxide and Nitrobenzene in *tert*-Butyl Alcohol.—A solution of 0.49 *N* potassium *tert*-butoxide in *tert*-butyl alcohol (10.0 ml) was placed in a 30-ml centrifuge tube and degassed by bubbling oxygen-free nitrogen through the solution. The tube was sealed with a septum and a mixture of nitrobenzene (264 mg, 2.15 mmol), *N*-benzylidenebenzylamine (210 mg, 1.08 mmol), and bicyclohexyl (81 mg) was injected with a calibrated syringe. The reaction mixture turned deep red and precipitated solid material. After 30 min at room temperature, the solids were separated by centrifugation and the supernatant was removed by syringe under nitrogen flush. The supernatant was added to a mixture of 50 ml of pentane and 100 ml of water. The pentane layer contained some dispersed solids, which were separated by filtration through a sintered glass filter after two 100-ml water washes. An amorphous brown solid (39 mg, mp 110–120°) was obtained and has not yet been identified. The filtrate was treated with more pentane and separated from the water used to wash the solids (some additional insoluble solid material was observed at this point) and the pentane layer was dried (Na_2SO_4). Partial evaporation of the pentane layer allowed gc analysis, which showed that 78% of the initial nitrobenzene had been lost, none (less than 0.5%) of the imine I remained, a peak with retention time equal to that of the benzaldehyde appeared, and some minor components of long retention time were also present.

The solids separated by centrifugation were washed with two 10-ml portions of degassed *tert*-butyl alcohol under nitrogen and after storage at 0° for 6 days were treated with 10 ml of DMSO. The resultant dark solution was sampled (*ca.* 50 μl) for esr, which gave the characteristic spectrum of nitrobenzene radical anion. The remaining solution was treated with oxygen (bubbled through until no solids were visible). This solution was poured into 100 ml of water and 50 ml of pentane. The pentane layer was separated, combined with a second 50-ml pentane extract, and dried over Na_2SO_4. Partial removal of the pentane by rotary evaporation after addition of 39.5 mg of hexadecane (by calibrated syringe) gave a sample for gc analysis which showed, after comparison with synthetic standards, the presence of 89.5 mg of nitrobenzene. This represents a 68% yield based on 1 mol of potassium nitrobenzenide/mol of I lost. It accounts for 55% of the nitrobenzene lost.

Acidification of the DMSO–water solution and extraction with ether gave 17 mg of brown gum.

Identification of Products from the Reaction of *N*-Neopentylidenebenzylamine (IV) with Oxygen as Catalyzed by Potassium *tert*-Butoxide and Nitrobenzene in *tert*-Butyl Alcohol.—A solution of potassium *tert*-butoxide in *tert*-butyl alcohol (143 ml, 0.49 *N*) was placed in a 500-ml flask and oxygen was bubbled through for several minutes. The reaction vessel and its contents were heated to 50° and a mixture of nitrobenzene (4.28 mg, 34.8 mmol) and IV (3.06 g, 17.4 mmol) was added. A rubber balloon containing oxygen was affixed and the reaction was allowed to proceed with occasional swirling for 209 hr. (In other cases stirring was used with no change in the qualitative outcome.) In the experiment presently being described, the amount of azoxybenzene, a major product of the anaerobic reaction, amounted to *ca.* 1% of the nitrobenzene present. In kinetic runs under oxygen, azoxybenzene was not observed.

The reaction mixture was cooled to room temperature and poured into a mixture of *ca.* 100 g of ice and 200 ml of water which contained pieces of solid carbon dioxide. This mixture, pH ~9, was extracted with two 100-ml portions of pentane. The pentane extracts were combined and dried over Na_2SO_4 and the pentane was removed by rotary evaporation to leave 4.61 g of a solid–liquid mixture. Re-treatment with pentane and filtration gave 0.76 g of solid which gave benzamide (undepressed mixture melting point) after ether washing. Gc analysis of the pentane-soluble material showed it to be mainly nitrobenzene containing some IV and V and small amounts of unidentified materials.

The aqueous layer was continuously extracted with ether for 24 hr. Drying (Na_2SO_4) and evaporation gave 0.9 g of solids which showed benzamide and pivalamide with a peak area ratio of 3.5:1. Both were collected from the gc effluent and identified by comparison of their infrared spectra with those of authentic samples. Some nitrobenzene (5–10% of mixture) was also present in this fraction. In two other experiments similar to the one being described, larger amounts of pivalamide relative to benzamide were observed but it was found difficult to reproduce the ratio. It is believed that this difficulty was due to the volatility of pivalamide. The total benzamide described above accounts for 60–70% of the benzyl groups in the starting imine.

The residual aqueous solution was acidified with concentrated hydrochloric acid and continuously extracted with ether for 1 week. The ether was dried (Na_2SO_4), concentrated, and treated with 438 mg of bicyclohexyl. Gc analysis showed a 45% yield of pivalic acid after comparison with synthetic standards. Direct gc analysis for benzoic acid proved impractical, so the mixture was treated with an excess of diazomethane in ether and the resultant mixture was found to contain an amount of methyl benzoate corresponding to 13% yield. In a separate experiment benzoic acid was isolated, purified, and compared to authentic material.

In summary, after correction for the presence of 8–10% of V, about 85% of oxidized IV shows up as benzoic acid or benzamide. The neopentylidene end of the molecule is converted either to pivalamide or pivalic acid, which together correspond to about 60% of oxidized IV. It is assumed that the balance of this material was lost in handling.

It was shown that pivalaldehyde was not present in the initial neutral extract by the addition of benzylamine, which would have reacted to increase the amount of IV. The only change observed was a decrease ln the amount of V which apparently reacts with benzylamine.

Acknowledgment.—We wish to thank the National Science Foundation for a grant (GP-17465) supporting this work.

Registry No.—I, 780-25-6; III, 14428-98-9; IV-h_2, 1775-74-2; IV-d_2, 40792-09-4; V, 7731-35-3; acetophenone, 98-86-2; benzylamine, 100-46-9; pivalaldehyde, 630-19-3; benzylamine-α-d_2, 15185-02-1; lithium aluminum deuteride, 14128-54-2; benzonitrile, 100-47-0; neopentylamine, 5813-64-9; benzaldehyde, 100-52-7; potassium nitrobenzenide, 40791-84-2; potassium *tert*-butoxide, 865-47-4; nitrobenzene, 98-95-3; oxygen, 7782-44-7.

The Alkaline Hydrolyses of *p*-Nitrophenyl Esters in the Presence of Polyelectrolytes[1]

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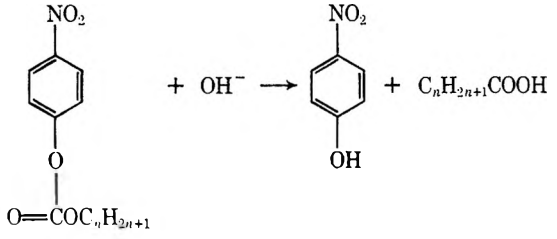
The rapid hydrolyses of *p*-nitrophenyl esters in a strongly alkaline media were followed using the stopped-flow technique in the presence of polyelectrolytes and in their absence. The esters used were *p*-nitrophenyl acetate, propionate, valerate, caprylate, laurate, and palmitate. The polyelectrolytes were poly(4-vinylpyridine) quaternized with ethyl, butyl, and benzyl halides, copolymer of 4-vinyl-*N*-benzylpyridinium chloride and 4-vinyl-*N*-cetylpyridinium bromide, and copolymer of diallyldiethylammonium chloride and sulfur dioxide. Cationic and anionic surfactants (cetyltrimethylammonium bromide and sodium lauryl sulfate) were also used. The ion–molecule reactions were accelerated with the hydrophobic cationic polyelectrolytes, and the strength of the acceleration increased with increasing hydrophobicity of esters and/or polyelectrolytes. The free energy, enthalpy, and entropy of activation were decreased by addition of the polyelectrolytes. The relative catalytic contributions of the electrostatic and hydrophobic interactions were discussed.

It is now well recognized that the reaction rates of many kinds of organic and inorganic reactions are strikingly influenced by polyelectrolytes.[2] The important contributions of hydrophobic interactions in a large number of organic reactions in solutions containing polyelectrolytes or micelle electrolytes have also been pointed out.[3-6]

In the present paper, we report additional data on the hydrophobic effects of polyelectrolytes using an ion–molecule reaction.



In this reaction, attractive interactions between the *p*-nitrophenyl ester and polyelectrolyte would be *hydrophobic*. On the other hand, those between hydroxide ions and macroion are certainly *electrostatic*. The relative magnitudes of the two kinds of interactions, therefore, may be compared by studying the reaction. We can also examine the hydrophobic interactions more systematically by changing n of the substrate ester (from 1 to 15 in the present study). Salts of poly(4-vinylpyridine) quaternized with alkyl halides of various numbers of methylene groups and polystyrene sulfonate were used as synthetic hydrophobic polyelectrolytes.

Results and Discussion

The hydrolyses were performed in aqueous media for *p*-nitrophenyl acetate (PNPA, $n = 1$), propionate (PNPPR, $n = 2$), and valerate (PNPV, $n = 4$). Those of *p*-nitrophenylcaprylate (PNPC, $n = 7$), laurate (PNPL, $n = 11$), and palmitate (PNPP, $n = 15$) were carried out in aqueous ethanol. The second-order rate constants, k_2, of the hydrolyses of PNPA, PNPV, and PNPP in the presence of various amounts of poly- or micelle electrolyte are portrayed in Figures 1–3. The k_2 values in the absence of polyelectrolytes or micelles were also plotted in the figures for the reader's convenience. The concentrations of the esters and the hydroxide ions are $4 \times 10^{-5} \sim 5 \times 10^{-5}$ M and $10^{-3} \sim 2.5 \times 10^{-2}$ M, respectively, and those of electrolytes $10^{-6} \sim 10^{-1}$ equiv $l.^{-1}$. The changes of pH during the reaction were not observed under the present experimental conditions. The results of PNPPR, PNPC, and PNPL were similar to those of the other esters and are not given here in order to save space.

Several important results were derived. First, the cationic polyelectrolytes having hydrophobic groups accelerated the hydrolyses, whereas those having no hydrophobic groups did not show such effects; *i.e.*, the accelerating effect of the polymer increases with increasing hydrophobicity of the polymer. The rate-enhancing actions are in the following order except for the PNPP system: DECS < C2PVP < C4PVP < BzPVP < C16BzPVP < CTABr, where DECS, C2PVP, C4PVP, BzPVP, and C16BzPVP indicate the copolymer of diethyldiallylammonium chloride and sulfur dioxide, poly(4-vinyl-*N*-ethylpyridinium bromide), poly(4-vinyl-*N*-butylpyridinium bromide), poly(4-vinyl-*N*-benzylpyridinium chloride), and copolymer of 4-vinyl-*N*-benzylpyridinium chloride (95%) and 4-vinyl-*N*-cetylpyridinium bromide (5%), respectively. In the case of PNPP, the rate-enhancing action of CTABr below $5 \times 10^{-3}M$ is not so large as that of cationic polysoaps such as C16BzPVP and BzPVP. The order is clearly the same as that of the hydrophobicity of the polyelectrolyte, and the same inequality was found to hold for the alkaline fading reactions of triphenylmethane dyes.[6] The hydroxide ions are attracted to the cationic polymer by the electrostatic attractive forces and the hydrophobic esters are also accumulated around the polymer by the hydrophobic attractive interactions. Thus, the cationic, hydrophobic polymer promotes the hydrolysis. Similar findings were observed for ester hydrolysis by using polysulfonic acid,[4] micelle-forming cationic detergents of various hydrophobicities,[7,8] and polyethylenimine derivatives.[9,10]

Second, hydrophobic polyelectrolyte was effective

(1) Presented at the 21st Annual Meeting of the Society of High Polymers, Tokyo, Japan, May 1972.

(2) See, for example, H. Morawetz, *Accounts Chem. Res.*, **3**, 354 (1970); N. Ise, *Advan. Polym. Sci.*, **7**, 536 (1970).

(3) (a) E. H. Cordes and R. B. Dunlop, *Accounts Chem. Res.*, **2**, 329 (1969); (b) E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).

(4) I. Sakurada, *J. Pure Appl. Chem.*, **16**, 263 (1968).

(5) T. Ueda, S. Harada, and N. Ise, *Polym. J.*, **3**, 476 (1972).

(6) T. Okubo and N. Ise, *J. Amer. Chem. Soc.*, **95**, 2293 (1973).

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(9) I. M. Klotz and V. H. Stryker, *J. Amer. Chem. Soc.*, **90**, 2717 (1968).

(10) G. P. Royer and I. M. Klotz, *J. Amer. Chem. Soc.*, **91**, 5885 (1969).

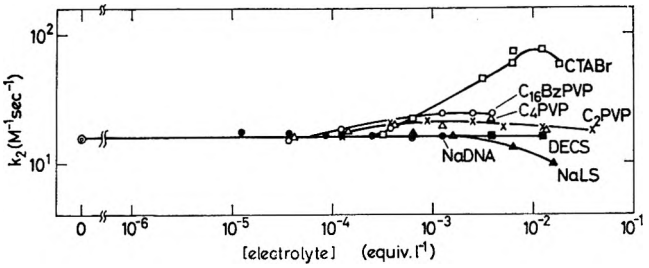

Figure 1.—Polyelectrolyte effect on the alkaline hydrolysis of PNPA at 30°: [PNPA] = 5×10^{-5} *M*, [NaOH] = 2.5×10^{-2} *M*.

in accelerating the reaction even in dilute concentration regions compared with surfactants; CTABr accelerated the reaction in the concentration above 10^{-4} *M*, whereas polyelectrolyte was effective at $10^{-6} \sim 10^{-5}$ equiv $l.^{-1}$ as is clearly shown in Figure 3. This is quite under standable because the charges and the hydrophobic groups are fixed to the main chain in the case of polyelectrolytes and cannot be separated by dilution from each other. The cmc of CTABr ($\sim 10^{-3}$*M* in pure water) would be expected to decrease upon the addition of a hydrophobic ester.[3b] Hence, one would expect CTABr to begin to catalyze the reaction at lower concentrations as the esters become more hydrophobic, which agrees with the observations.

Third, the strength of the rate-enhancing action of the polyelectrolytes is most marked for the hydrolysis of PNPP and least for PNPA with the order PNPA < PNPPR < PNPV < PNPC < PNPL < PNPP. This feature has already been demonstrated for the hydrolyses in the presence of surfactant, in which the concentration of hydroxide ions was extremely low compared with that in the present work.[11,12] The relative strength of the rate enhancement by C16BzPVP of the hydrolysis is shown in Table I, where k_{20} is the rate

TABLE I
RATE ENHANCEMENT BY C16BzPVP OF THE ALKALINE HYDROLYSES OF *p*-NITROPHENYL ESTERS

Concn of C16BzPVP, equiv $l.^{-1}$	k_2/k_{20}					
	$n = 1^a$	2^a	4^a	7^b	11^c	15^d
1.25×10^{-5}	1.00	1.15	1.40			15.0
1.25×10^{-4}	1.12	1.15	1.58	1.63	2.95	43.9
3.75×10^{-4}	1.14	1.38	1.96	2.39	5.32	80.2
1.25×10^{-3}	1.34	1.57	2.47	3.98	21.4	135
3.75×10^{-3}	1.46	1.59	3.57	16.9	112	140

[a] [Ester] = 5×10^{-6} *M*, [OH^-] = 2.5×10^{-2} *M*, at 30°, in pure water. [b] [Ester] = 5×10^{-6} *M*, [OH^-] = 2.5×10^{-2} *M*, at 25°, in 15% EtOH–H_2O. [c] [Ester] = 5×10^{-5} *M*, [OH^-] = 2.5×10^{-2} *M*, at 25°, in 22.5% EtOH–H_2O. [d] [Ester] = 4×10^{-5} *M*, [OH^-] = 10^{-3} *M*, at 30°, in 30% EtOH–H_2O.

constant without the polyelectrolyte. As is clear in the table, the larger the *n* values of esters, the stronger the rate enhancement. The maximum acceleration factor for the hydrolysis of PNPP is about 150, whereas that for PNPA is only 1.5. The factor for PNPP probably would become much larger if the reaction could be carried out in pure water, since ethanol is considered to be a breaker of the hydrophobic bonds between ester and catalyst.

(11) C. Gitler and A. Ochoa-Solano, *J. Amer. Chem. Soc.*, **90**, 5004 (1968).
(12) C. A. Blyth and J. R. Knowles, *J. Amer. Chem. Soc.*, **93**, 3021 (1971).

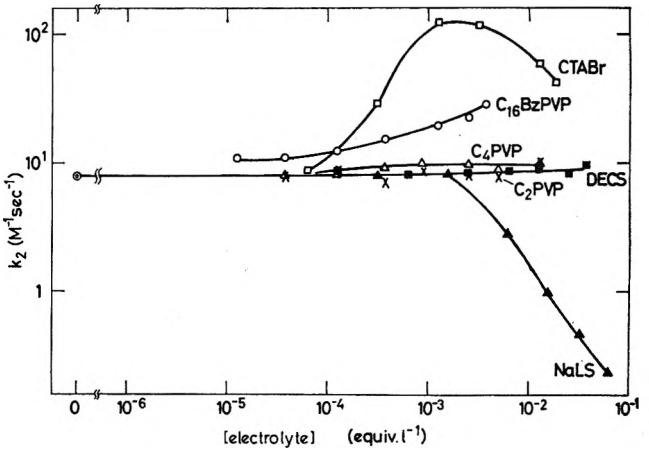

Figure 2.—Polyelectrolyte effect on the alkaline hydrolysis of PNPV at 30°: [PNPV] = 5×10^{-5} *M*; [NaOH] = 2.5×10^{-2} *M*.

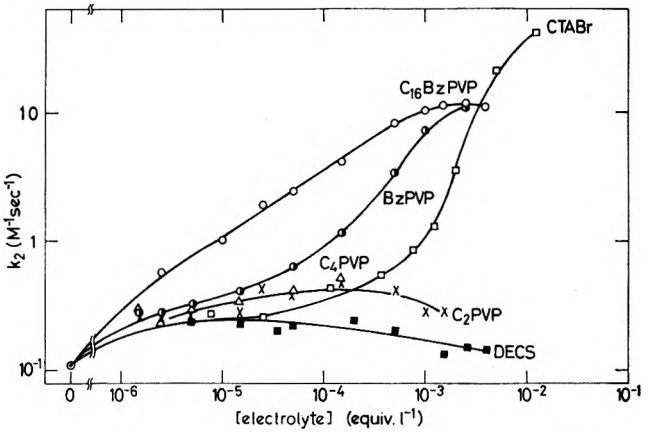

Figure 3.—Polyelectrolyte effect on the alkaline hydrolysis of PNPP at 30° in 30% ethanol–H_2O: [PNPP] = 4×10^{-5} *M*, [NaOH] = 10^{-3} *M*.

The activation parameters, namely the free energy ($\Delta G^{\pm}$), enthalpy ($\Delta H^{\pm}$), and entropy ($\Delta S^{\pm}$) of activation, are given in Table II for the alkaline hydrolysis

TABLE II
ACTIVATION PARAMETERS FOR THE ALKALINE HYDROLYSIS OF PNPL IN 22.5% ETHANOLIC AQUEOUS SOLUTION AT 30° [a]

Electrolyte	Concn of electrolyte, equiv $l.^{-1}$	$\Delta G^{\pm}$, kcal mol^{-1}	$\Delta H^{\pm}$, kcal mol^{-1}	$\Delta S^{\pm}$, cal deg^{-1} mol^{-1}
None	0	18.0	10.9	−23
C16BzPVP	1.67×10^{-3}	14.7	5.3	−31
CTABr	2.5×10^{-3}	14.6	4.8	−32

[a] [PNPL] = 5×10^{-5} *M*, [NaOH] = 2.5×10^{-2} *M*.

of PNPL in the presence of C16BzPVP and CTABr and in their absence. As was usually found,[13] the $\Delta S^{\pm}$ values are strongly negative. All three parameters were decreased by the electrolytes. It should be noted that the $\Delta H^{\pm}$ was sharply decreased by the electrolyte, as was the case for interionic reactions in the presence of polyelectrolytes.[2,14] The decrease in $\Delta S^{\pm}$ suggests that the acceleration is due to the enthalpic loss.

(13) K. J. Laidler, "Chemical Kinetics," 2nd ed, McGraw-Hill, London, 1965.
(14) N. Ise and F. Matsui, *J. Amer. Chem. Soc.*, **90**, 4242 (1968).

Experimental Section

Materials.—PNPA obtained from Nakarai Chemicals Co., Kyoto, Japan, was further purified by recrystallization until it was nearly colorless (mp 78°). PNPPR, PNPV, PNPC, and PNPL obtained from Sigma Chemicals Co. were used without further purification. PNPP was a guaranteed reagent from Nakarai Chemicals Co. The details about the preparation of the polymers, namely C2PVP, C4PVP, BzPVP, C16BzPVP, and DECS, were described in the preceding paper.[8] The degree of polymerization of the parent poly(4-vinylpyridine) is 3800. The characterization of NaDNA was also described before.[6] NaLS and CTABr were commercially available. Deionized water was used for the preparation of the solutions of esters and polymer catalysts.

Kinetic Measurements.—Reaction rates were obtained from the change in absorbance at 400 nm owing to release of *p*-nitrophenoxide ion. The rapid reaction was followed using a Hitachi stopped-flow spectrophotometer, Model RSP-2, with a Hitachi memoriscope Model V-018. The slow ractions were monitored using a Hitachi spectrophotometer Model EPS-3T.

Registry No.—PNPA, 830-03-5; PNPPR, 1956-06-5; PNPV, 1956-07-6; PNPC, 1956-10-1; PNPL, 1956-11-2; PNPP, 1492-30-4; C2PVP, 25619-82-3; C4PVP, 25703-28-0; BzPVP, 30109-97-8; C16BzPVP, 40780-43-6; DECS, 27577-32-8; CTABr, 57-09-0; NaLS, 151-21-3.

Proton Nuclear Magnetic Resonance Spectra of 1-Substituted Acenaphthenes and Other Systems of Well-Defined Geometry[1a]

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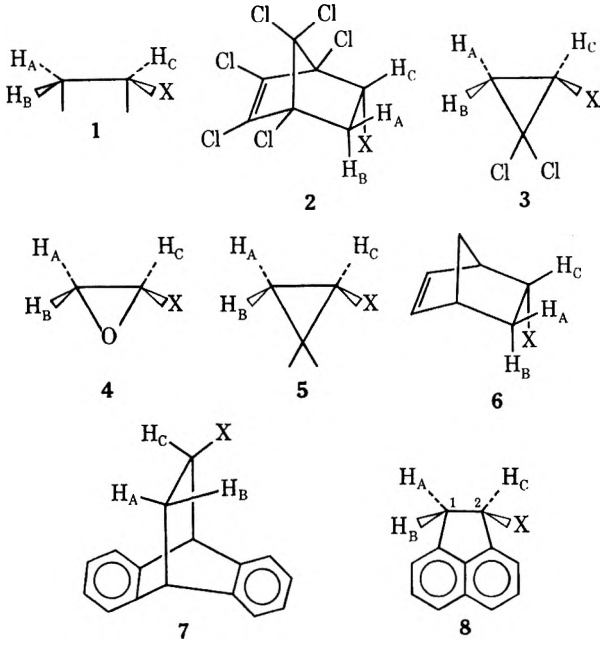
The pmr spectra of 22 1-substituted acenaphthenes were analyzed and the published nmr data for series of hexachlorobicyclo[2.2.1]heptenes, oxiranes, 1,1-dichlorocyclopropanes, and dibenzobicyclo[2.2.2]octadienes were extended by the analysis of the parent compound using ^{13}C satellites. The above data enable us to derive the following conclusions. (1) For the common range of functional groups, the dependence of vicinal and geminal coupling constants on the "electronegativity" of the substituent X is complex. However, it appears likely that empirical "substituent effects" can be used predictively. (2) A wide variety of substituents shield the vicinal protons eclipsed by them relatively to those trans to them. With some substituents ($-COCH_3$, $-COOH$, $-COOMe$, $-CONH_2$, $-N^+Me_3$, $-CHO$) the opposite effect may be observed. (3) By comparison with unsubstituted compounds, trans vicinal protons and geminal protons are deshielded by all substituents encountered here, except $-SiMe_3$. The cis vicinal protons may be either shielded or deshielded. (4) No encompassing theoretical analysis of the observed shifts was possible. However, by restricting the data to selected substituents it has been shown that the shift of the geminal hydrogen induced by a given substituent depends on the substrate. A Hammett-type relationship has been proposed which should prove useful for estimation of chemical shifts. An interpretation of this observation in terms of the inductive effect is presented. (5) For substituents limited to first-row elements, both vicinal hydrogens are shifted to about the same extent, consistent with either electric field or inductive effects. In addition, the eclipsed vicinal hydrogen shows a substantial upfield shift which is not explicable by any current theory. A new interpretation in terms of backbonding and a Karplus type relationship is suggested.

To explore the influence of substituents on chemical shifts and coupling constants, it is necessary to use molecules of reasonably well-defined stereochemistry. System **1** represents one class of compounds where H_A and H_C are approximately eclipsed and X is any substituent of interest in proton magnetic resonance studies. Clearly, system **1** can be incorporated only into flat, rigid rings and extensive systematic studies have so far been confined to hexachlorobicyclo[2.2.1]heptenes (**2**)[2a] and their 7,7-difluoro derivatives,[2b] 1,1,dichlorocyclopropanes (**3**),[3] oxiranes (**4**),[3] cyclopropanes (**5**),[4,5] and norbornenes (**6**).[6] A fairly large collection of data is also available[7] for dibenzobicyclo[2.2.2]octadienes (**7**), and some general studies dealing with the effects of substituents on coupling constants[8] are pertinent.

This work deals with the nmr parameters for fragment **1** in 22 1-substituted acenaphthenes (**8**) and with the extension of data for systems **2**, **3**, **4**, and **7** by the analysis of the nmr spectra of the parent compounds (X = H) for each series. The principal purpose of the present study was the exploration of previously pro-



(1) (a) Abstracted in part from the Ph.D. thesis of P. W. Westerman, University of Sydney, 1970; (b) University of Sidney; (c) Purdue University; (d) Varian Associates.

(2) (a) K. L. Williamson, *J. Amer. Chem. Soc.*, **85**, 516 (1963); (b) K. L. Williamson and J. C. Fenstermaker, *ibid.*, **90**, 342 (1968).

(3) K. L. Williamson, C. A. Lanford, and C. R. Nicholson, *ibid.*, **86**, 762 (1964).

(4) K. M. Crecely, V. S. Watts, and J. H. Goldstein, *J. Mol. Spectrosc.*, **30**, 184 (1969).

(5) P. A. Scherr and J. P. Oliver, *ibid.*, **31**, 109 (1969).

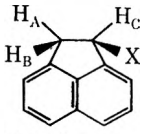
(6) P. Laszlo and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **85**, 2709 (1963).

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

(8) S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969).

TABLE I

NMR DATA FOR 1-SUBSTITUTED ACENAPHTHENE DERIVATIVES[a]

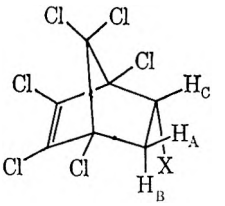


Registry no.	No.	X	E_X[b] c	E_X[b] d	E_X[b] e	Chemical shifts, ppm (ex TMS)[f] H_A	H_B	H_C	$\delta_A - \delta_B$	Chemical shifts from parent (X = H), ppm H_A	H_B	H_C	Coupling constants, Hz J_{AB}	J_{AC}	J_{BC}
83-32-9	1	H	1.78	2.00	1.9	3.36	3.36	3.36	0	0.0	0.0	0.0	—	9.2 ± 0.1	3.8 ± 0.1
35998-76-6	2	CMe_3[g]	2.02	2.20	2.1	3.40	3.30	3.53	0.10	−0.04	0.06	−0.17	−17.88 ± 0.02	8.25 ± 0.02	3.28 ± 0.02
18086-45-8	3	Me	2.07	2.23	2.2	3.43	2.74	3.53	0.69	−0.09	0.62	−0.17	−17.4 ± 0.2	8.1 ± 0.05	3.8 ± 0.1
40745-35-5	4	CH_2COMe	2.24	2.38	2.3	3.67	2.96	4.07	0.71	−0.31	0.40	−0.71	−17.5 ± 0.3	8.0 ± 0.3	3.5 ± 0.3
7508-18-1	5	CH_2COOH	2.25	2.38	2.3	3.69	3.10	4.11	0.59	−0.33	0.26	−0.75	−17.1 ± 0.3	8.0 ± 0.3	3.0 ± 0.3
40745-37-7	6	$CH(COO^-)_2$[h]	2.35	2.47	2.4	3.71	3.15	4.33	0.56	−0.35	0.21	−0.97	−18.0 ± 0.3	8.0 ± 0.3	3.5 ± 0.3
40745-38-8	7	$CH(COOEt)_2$[i]	2.40	2.51	2.5	3.60	3.32	4.37	0.28	−0.24	0.04	−1.01	−17.8	8.6	3.2
						(3.66)	(3.31)	(4.35)	(0.35)						
40745-39-9	8	CN	2.49	2.58	2.5	3.82	3.72	4.55	0.10	−0.46	−0.36	−1.19	−17.60 ± 0.02	9.02 ± 0.03	5.14 ± 0.03
								(4.42)							
40745-40-2	9	$CONH_2$[j]	2.53	2.62	2.6	3.47	3.73	4.39	−0.26	−0.11	−0.37	−1.03	−17.57 ± 0.01	8.02 ± 0.02	3.40 ± 0.02
40745-41-3	10	COOMe	2.58	2.66	2.6	3.52	3.82	4.49	−0.30	−0.16	−0.46	−1.13	−17.8 ± 0.1	8.8 ± 0.1	4.1 ± 0.1
6833-51-8	11	COOH	2.60	2.68	2.6	3.57	3.82	4.55	−0.25	−0.21	−0.46	−1.19	−17.52 ± 0.00	8.73 ± 0.00	3.71 ± 0.00
40745-43-5	12	Ph	2.75	2.80	2.8	3.82	3.26	4.71	0.56	−0.46	0.10	−1.35	−17.51 ± 0.04	8.57 ± 0.04	4.24 ± 0.04
						(3.82)	(3.26)	(4.71)	(0.56)						
40745-44-6	13	NH_2	2.91	2.93	2.9	3.64	2.88	4.71	0.76	−0.28	0.48	−1.35	−17.42 ± 0.02	7.47 ± 0.02	3.35 ± 0.02
						(3.70)	(2.93)	(4.75)	(0.77)						
24171-73-1	14	Br	2.96	3.10	3.0	3.84	3.65	5.71	0.19	−0.48	−0.29	−2.35	−18.63 ± 0.03	7.27 ± 0.04	2.21 ± 0.04
								(5.83)							
40745-46-8	15	CPh_3[k]	3.07	3.06	3.1	3.90	3.10	5.44	0.80	−0.54	0.26	−2.08	−17.56 ± 0.07	8.28 ± 0.07	2.43 ± 0.07
40745-47-9	16	$^+NMe_3\ Br^-$[l]	3.17	3.15	3.2	3.74	3.97	5.61	−0.25	−0.38	−0.61	−2.25	−19.08 ± 0.05	8.21 ± 0.06	1.56 ± 0.06
40745-48-0	17	NHCOMe	3.21	3.18	3.2	3.89	3.08	5.92	0.81	−0.53	0.28	−2.56	−17.80 ± 0.00	7.46 ± 0.00	2.84 ± 0.00
40745-49-1	18	Cl	3.25	3.21	3.2	3.82	3.52	5.67	0.30	−0.46	−0.16	−2.31	−18.00 ± 0.00	7.37 ± 0.00	2.44 ± 0.00
						(3.99)	(3.65)	(5.80)	(0.34)						
21857-35-2	19	OMe	3.30	3.25	3.3	3.64	3.31	5.39	0.33	−0.28	0.05	−2.03	−17.80 ± 0.00	7.10 ± 0.00	2.51 ± 0.00
						(3.51)	(3.24)	(5.30)	(0.27)						
6306-07-6	20	OH	3.43	3.36	3.4	3.64	3.11	5.59	0.53	−0.28	0.25	−2.23	−17.80 ± 0.00	7.13 ± 0.00	2.57 ± 0.00
						(3.71)	(3.14)	(5.58)	(0.57)						
14966-36-0	21	OCOMe	3.74	3.60	3.7	3.68	3.18	6.50	0.50	−0.32	0.18	−3.14	−17.50 ± 0.00	7.24 ± 0.00	2.46 ± 0.00
						(3.63)	(3.19)	(6.42)	(0.44)						
3798-81-0	22	F[m]	3.92	3.76	3.9								−18.30	6.68	1.49

[a] The data refer to *ca.* 10% solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are believed to be significant to ±0.02 ppm and coupling constants to ±0.2 Hz, unless otherwise indicated. [b] The chemical shift data for ethyl derivatives EtX used to calculate the electronegativity of X (E_X) are taken from the previously prepared compilation (ref 10b) unless otherwise stated. [c] Dailey electronegativity (ref 9). [d] Muller electronegativity: J. C. Muller, *Bull. Soc. Chim. Fr.*, 1815 (1964). [e] Electronegativity value accepted in this work. [f] Figures in parentheses refer to chemical shifts in 1–3% solutions in CCl_4. [g] Chemical shifts of Me_3CCH_2Me used in calculating electronegativities were obtained from the work of Bartz and Chamberlain: K. W. Bartz and N. F. Chamberlain, *Anal. Chem.*, **36**, 2151 (1964). [h] Data for solution in D_2O containing excess potassium carbonate. Chemical shifts are from trimethylsilylpropanesodium sulfonate (TMPS). Under the same conditions the chemical shifts in $MeCH_2CH(COO^-)_2$ are δ_{Me} 0.85, δ_{CH_2} 1.67 ppm. [i] Chemical shifts in $MeCH_2CH(COOEt)_2$ are δ_{Me} 0.95, δ_{CH_2} 1.86 ppm (CCl_4 solution). [j] Approximately 5% solution in CCl_4 (90%) and DMSO (10%). [k] 1-Tritylacenaphthene [G. Wittig, W. Tochtermann, and B. Knickel, *Angew. Chem., Int. Ed. Engl.*, **7**, 139 (1968); W. Tochtermann and B. Knickel, *Chem. Ber.*, **102**, 3508 (1969)] was kindly donated by Dr. W. Tochtermann, Heidelberg. Chemical shifts in 1,1,1-triphenylpropane are δ_{Me} 0.78, δ_{CH_2} 2.66 ppm ($CDCl_3$ and CCl_4). [l] In D_2O chemical shifts from TMPS. In both diethyldimethylammonium iodide and triethylmethylammonium iodide $\delta_{Me} - \delta_{CH_2} = 2.04$ ppm (in D_2O). [m] Data from Dr. L. D. Hall, University of British Columbia.

TABLE II

NMR DATA FOR HEXACHLOROBICYCLO[2.2.1]HEPTENES[a]

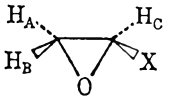


Registry no.	No.	X[i]	E_X[b] c	E_X[b] d	E_X[b] e	Chemical shifts, ppm (ex TMS) H_A	H_B	H_C	$\delta_A - \delta_B$	Chemical shifts from parent (X = H), ppm H_A	H_B	H_C	Coupling constants, Hz J_{AB}	J_{AC}	J_{BC}
22039-38-9	1	H	1.78	2.00	1.9	2.49	2.00	2.49	0.49	0	0	0	−12.42	9.73[f]	3.81
40745-55-9	3	CH_3[g]	2.07	2.23	2.2	2.63	1.58	2.86	1.05	−0.14	0.42	−0.37	−12.18	8.81	3.91
19095-26-2	8	CN	2.49	2.58	2.5	2.70	2.15	3.40	0.55	−0.21	−0.15	−0.91	−12.6	9.3	4.6
2157-20-2	11	COOH	2.60	2.68	2.6	2.72	2.43	3.62	0.29	−0.23	−0.43	−1.13	−12.6	8.5	4.4
17064-54-9	12	Ph	2.75	2.80	2.8	2.87	2.38	3.87	0.49	−0.38	−0.38	−1.38	−12.7	8.9	4.2
5202-36-8	18	Cl	3.25	3.21	3.2	3.08	2.22	4.72	0.86	−0.59	−0.22	−2.23	−13.2	8.0	3.2
19095-29-5	20	OH	3.43	3.36	3.4	2.78	1.90	4.63	0.88	−0.29	0.10	−2.14	−12.6	7.4	2.4
19095-28-4	21	OCOMe	3.74	3.60	3.7	2.95	1.90	5.50	1.05	−0.46	0.10	−3.01	−13.3	7.6	2.5
40745-62-8	22	F[h]	3.92	3.76	3.9	2.85	2.11	5.31	0.74	−0.36	−0.11	−2.82	−13.3	7.19	1.82

[a] The data refer to 10% solutions in CS_2 unless otherwise indicated. Chemical shifts are believed to be significant to ±0.02 ppm and coupling constants to ±0.2 Hz. [b] See footnote *b*, Table I. [c] Dailey electronegativity. [d] Muller electronegativity. [e] Electronegativity value accepted in this work. [f] $J_{exo,exo} \cdot J_{endo,endo}$ = 9.16 Hz (*cf.* text). [g] A. Dean and S. Sternhell, unpublished observations. [h] Data for 5 mol % solution in cyclohexane: S. L. Smith, University of Kentucky, private communication. [i] Reference 2.

TABLE III

NMR DATA FOR MONOSUBSTITUTED ETHYLENE OXIDES[a]



Registry no.	No.	X	E_X[b] c	E_X[b] d	E_X[b] e	Chemical shifts, ppm (ex TMS) H_A	H_B	H_C	$\delta_A - \delta_B$	Chemical shifts from parent (X = H), ppm H_A	H_B	H_C	Coupling constants, Hz J_{AB}	J_{AC}	J_{BC}
75-21-8	1	H	1.78	2.00	1.9	2.49 (2.54)[g]	2.49 (2.54)[g]	2.49 (2.54)[g]	0	0	0	0	−6.26 ± 1.6	4.43[f]	3.08[f]
75-56-9	3	Me[h]	2.07	2.23	2.1	2.59	2.28	2.85	0.31	−0.10	0.21	−0.36	5.37[f]	3.88[f]	2.57[f]
4538-51-6	8	CN[i]	2.49	2.58	2.5	3.12	3.00	3.50	0.12	−0.63	−0.51	−1.01	5.5	4.2	2.5
503-11-7	11	COOH[i]	2.60	2.68	2.6	2.99	2.93	3.48	0.06	−0.50	−0.44	−0.99	6.3	5.0	1.9
765-34-4		CHO[i]	2.69	2.75	2.7	3.17	3.10	3.35	0.07	−0.68	−0.61	−0.86	5.5	4.9	2.0
4401-11-0		$COCH_3$[j]	2.75	2.80	2.8	2.96	2.84	3.28	0.12	−0.47	−0.35	−0.79	5.7	4.3	2.7
96-09-3	12	Ph[i]	2.75	2.80	2.8	2.82	2.52	3.61	0.30	−0.33	−0.03	−1.12	5.7	4.0	2.5
7763-77-1	18	Cl[i]	3.25	3.21	3.2	2.83	2.75	4.90	0.08	−0.34	−0.26	−2.41	4.7	2.7	1.4
36099-39-5	21	OCOMe[i]	3.74	3.60	3.7	2.76	2.58	5.33	0.18	−0.27	−0.09	−2.84	4.5	2.2	1.4

[a] The data refer to 10% solutions in CS_2 unless otherwise indicated. Chemical shifts are believed to be significant to ±0.02 ppm and coupling constants to ±0.2 Hz. [b] See footnote *b*, Table I. [c] Dailey electronegativity. [d] Muller electronegativity. [e] Electronegativity value accepted in this work. [f] Probable error ≤0.01. [g] E. Lippert and H. Prigge, *Ber. Bunsenges. Ges.*, 67, 415 (1963). [h] Chemical shift data for CCl_4 solution [G. Allen, D. J. Blears, and K. H. Webb, *J. Chem. Soc.*, 810 (1965)]; coupling constants for neat liquid [D. D. Elleman, S. L. Manatt, and C. D. Pearce, *J. Chem. Phys.*, 42, 650 (1965)]. [i] Reference 3. [j] Values for CCl_4 solution [J. L. Pierre, P. Chautemps, and P. Arnaud, *C. R. Acad. Sci.*, 261, 4025 (1965)].

posed correlations[8] between geminal (J_{AB}) and vicinal (J_{AC} and J_{BC}) coupling constants in fragment **1** with electronegativity[9] and of the relative shielding of the β protons (H_A and H_B) by the substituent X. Scattered observations about the latter effect can be found in the literature[10a] and the substituents in this work were chosen to explore the effects of commonly encountered functional groups with the view of obtaining correlations useful in structural investigations.

Results and Discussion

The nmr data for acenaphthenes are presented in Table I, for hexachlorobicyclo[2.2.1]heptenes in Table II, for oxiranes in Table III, for 1,1-dichlorocyclopropanes in Table IV, and for dibenzobicyclo[2.2.2]octadienes in Table V. With the exception of the parameters for the parent hydrocarbons, most of the data in Tables II–V are taken from the literature and converted to units used to describe the acenaphthene series to allow direct comparison between the various series. Table VI gives nmr parameters for monosubstituted cyclopropanes abstracted from literature.[4,5,11] Entry numbers in each table refer to the same substituents.

A. Analysis of Nmr Spectra.—With the exception of entries 1–3 (Table I) the nmr spectra of 1-substituted acenaphthenes gave well-defined patterns for signals assigned to protons at C-1 and C-2. In all cases the relevant resonances were further split by coupling with aromatic protons[8] and analyses were performed on 100-MHz spectra with the latter decoupled. The spectra of 1-substituted acenaphthenes where the group X had

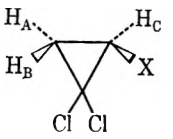
(9) J. R. Cavanaugh and B. P. Dailey, *J. Chem. Phys.*, **34**, 1099 (1961).

(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969: (a) Chapter 3-8; (b) p 164; (c) Chapters 4-1 and 4-2; (d) p 64; (e) Chapter 2-2.

(11) R. J. Crawford and G. L. Erickson, *J. Amer. Chem. Soc.*, **89**, 3907 (1967).

TABLE IV

NMR DATA FOR 2-SUBSTITUTED 1,1-DICHLOROCYCLOPROPANES[a]

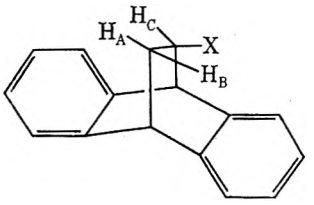


Registry no.	No.	X	E_X[b] c	E_X[b] d	E_X[b] e	Chemical shifts, ppm (ex TMS) H_A	H_B	H_C	$\delta_A - \delta_B$	Chemical shifts from parent (X = H), ppm H_A	H_B	H_C	Coupling constants, Hz J_{AB}	J_{AC}	J_{BC}
2088-35-9	1	H	1.78	2.00	1.9	1.45	1.45	1.45	0	0	0	0	−4.99[f]	11.25[f]	7.99[f]
													(−6.0)[g]	(11.2)[g]	(8.0)[g]
3591-38-6		$SiMe_3$	1.80	1.76	1.8	1.43	1.11	0.58	0.32	0.02	0.34	0.87	−4.9	12.6	9.6
5365-14-0	11	COOH[h]	2.60	2.68	2.6	1.87	2.02	2.52	−0.15	−0.42	−0.57	−1.07	−6.8	11.0	6.8
2415-80-7	12	Ph[h]	2.75	2.80	2.8	1.85	1.73	2.80	0.12	−0.40	−0.28	−1.35	−7.3	10.5	8.6
40745-72-0	14	Br[h]	2.96	3.10	3.0	2.08	1.58	3.45	0.50	−0.63	−0.13	−2.00	−8.6	9.4	6.6
17355-81-6	19	OMe[h]	3.30	3.25	3.3	1.67	1.52	3.62	0.15	−0.22	−0.07	−2.17	−8.4	7.9	5.3
3591-44-4	21	OCOMe[h]	3.74	3.60	3.7	1.84	1.58	4.28	0.26	−0.39	−0.13	−2.83	−9.1	8.0	5.4

[a] The data refer to 10% solutions in CS_2 unless otherwise indicated. Chemical shifts are believed to be significant to ±0.02 ppm and coupling constants to ±0.2 Hz. [b] See footnote *b*, Table I. [c] Dailey electronegativity. [d] Muller electronegativity. [e] Electronegativity value accepted in this work. [f] Probable error ≤0.03. [g] D. J. Patel, M. E. H. Howden, and J. D. Roberts, *J. Amer. Chem. Soc.*, **85**, 3218 (1963). [h] Reference 3.

TABLE V

NMR DATA FOR 7-SUBSTITUTED DIBENZOBICYCLO[2.2.2]OCTADIENES[a]

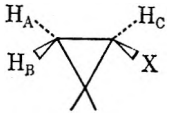


Registry no.	No.	X	E_X[b] c	E_X[b] d	E_X[b] e	Chemical shifts, ppm (ex TMS) H_A	H_B	H_C	$\delta_A - \delta_B$	Chemical shifts from parent (X = H) ppm H_A	H_B	H_C	Coupling constants, Hz J_{AB}	J_{AC}	J_{BC}
5675-64-9	1	H	1.78	2.00	1.9	1.68[f]	1.68[f]	1.68[f]	0	0	0	0	–	11.1 ± 0.1	4.4 ± 0.1
6372-65-2	13	NH_2[g]	2.91	2.93	2.9	2.14	0.97	3.11	1.17	−0.46	0.71	−1.43	−12.3	9.5	3.0
19371-69-8	16	$^+NMe_3\ ^-Br$[h,i]	3.17	3.15	3.2	1.90	1.75	3.5	0.15	−0.22	−0.07	−1.8	−14.2	10.0	5.8
6476-45-5	18	Cl[g]	3.25	3.21	3.2	2.40	1.75	4.14	0.65	−0.72	−0.07	−2.46	−14.0	8.0	2.5
1521-59-1	20	OH[g]	3.43	3.36	3.4	2.19	1.18	3.94	1.01	−0.51	0.50	−2.26	−12.8	8.5	3.0
2975-83-9		OTs[g]	3.67	3.55	3.6	2.08	1.50	4.88	0.58	−0.40	0.18	−3.20	−13.8	9.0	3.5
1871-17-6	21	OCOMe[g]	3.74	3.60	3.7	2.25	1.41	4.90	0.84	−0.57	0.27	−3.22	−13.0	8.8	3.3

[a] Unless otherwise stated the data refer to CCl_4 solutions. Chemical shifts are significant to ±0.02 ppm and coupling constants to ±0.2 Hz. [b] See footnote *b*, Table I. [c] Dailey electronegativity. [d] Muller electronegativity. [e] Electronegativity value accepted in this work. [f] K. Tori, Y. Takano, and K. Kitahonoki, *Chem. Ber.*, **97**, 2798 (1964). [g] Reference 7. [h] Data for solution in CF_3COOH. [i] Y. Terui, K. Aono, and K. Tori, *J. Amer. Chem. Soc.*, **90**, 1069 (1968).

TABLE VI

NMR DATA FOR MONOSUBSTITUTED CYCLOPROPANES[a]



Registry no.	No.	X	E_X[b] c	E_X[b] d	E_X[b] e	Chemical shifts, ppm H_A	H_B	H_C	$\delta_A - \delta_B$	Chemical shifts from parent (X = H), ppm H_A	H_B	H_C	Coupling constants, Hz J_{AB}	J_{AC}	J_{BC}
75-19-4	1	H[f]	1.78	2.00	1.9	0.20	0.20	0.20	0	0	0	0	−4.34	8.97	5.58
594-11-6	3	Me[g]	2.07	2.23	2.2	0.40	−0.06	0.65	0.46	−0.20	0.26	−0.45	2.5	7.5	4.0
5500-21-0	8	CN[f]	2.49	2.58	2.5	0.94	0.94	1.36	0.00	−0.74	−0.74	−1.16	−4.72	8.43	5.12
1759-53-1	11	COOH[f]	2.60	2.68	2.6	0.91	1.01	1.59	−0.10	−0.71	−0.81	−1.39	−4.00	8.04	4.57
765-43-5		$COCH_3$[f]	2.75	2.80	2.8	0.81	0.85	1.96	−0.04	−0.61	−0.65	−1.76	−3.41	7.96	4.55
765-30-0	13	NH_2[f]	2.91	2.93	2.9	0.32	0.20	2.23	0.12	−0.12	0.00	−2.03	−4.29	6.63	3.55
4333-56-6	14	Br[f]	2.96	3.10	3.0	0.96	0.81	2.83	0.15	−0.76	−0.61	−2.63	−6.12	7.13	3.80
7393-45-5	18	Cl[f]	3.25	3.21	3.2	0.87	0.74	2.96	0.13	−0.67	−0.54	−2.76	−6.01	7.01	3.58
16545-68-9	20	OH[h]	3.43	3.36	3.4	0.59	0.34	3.35	0.25	−0.39	−0.14	−3.15	−5.43	6.19	2 94
1959-79-1	22	F[i]	3.92	3.76	3.9	0.69	0.27	4.32	0.42	−0.49	−0.07	−4.12	−6.69	5.89	2.39

[a] The data refer to neat liquids unless otherwise stated. [b] See footnote *b*, Table I. [c] Dailey electronegativity. [d] Muller electronegativity. [e] Electronegativity value accepted in this work. [f] Reference 4. [g] Data for chloroform solution [R. J. Crawford and G. L. Erickson, *J. Amer. Chem. Soc.*, **89**, 3907 (1967)]. The data presented here were not used for plots of *J vs.* E_R etc., because of the unlikely value quoted for J_{gem} and lack of published details concerning the analysis of the nmr spectrum. [h] Data (ref 5) for 13 mol % solution in benzene. [i] Data (ref 5) for 8 mol % solution in 38 mol % benzene and 54 mol % trichlorofluoromethane.

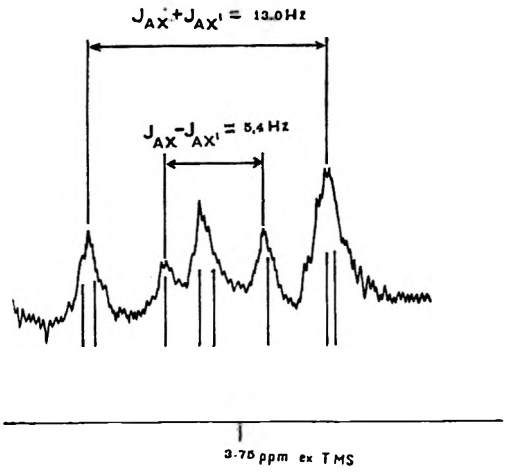


Figure 1.—Downfield ^{13}C satellite of the resonance assigned to benzylic protons in the 100-MHz spectrum of acenaphthene, with decoupling of the aromatic protons. The theoretical spectrum was generated (LAOCN3, stage I) for the AA'XX' system with $J_{AA'} = J_{XX'} = -1.8$, $J_{AX} = 9.2$, $J_{AX'} = 3.8$, and $\nu_{AX} = 64.5$ Hz (*i.e.*, $^1/_2J_{^{13}C,H}$), 10% w/v solution in $CDCl_3$.

protons coupled to H_C (entries 4–7, Table I) were analyzed as ABX systems with coupling to protons in group X considered as first-order perturbations, which was justified by the $\Delta\nu/J$ ratios involved.

The nmr spectra of the remaining 1-substituted acenaphthenes (entries 8–21, Table I) were analyzed as ABC systems using the iterative computer program LAOCN3[12] executed on an IBM 7040/1401 in the Basser Computing Laboratory, School of Physics, University of Sydney. The errors quoted are probable errors appearing in the final iteration in the computer output.

Acenaphthene.—The ^{13}C satellites (Figure 1) of the resonance assigned to the benzylic protons were analyzed as an AA'XX' system with $\nu_{AX} = {}^1/_2J_{^{13}CH}$ by the method of Mortimer,[13] it being assumed that the signs of J_{AX} and $J_{AX'}$ are the same.[8] The experimental $J_{AX} + J_{AX'}$ and $J_{AX} - J_{AX'}$ values shown in Figure 1 are averages of five runs on each of the two satellites and are estimated to be significant to ±0.1 Hz. The theoretical AA'BB' spectrum shown in Figure 1 was generated with the LAOCN3 stage I (noniterative) program using the values for J_{AB} and $J_{AB'}$ obtained by measurement, $\nu_{AB} = {}^1/_2J_{^{13}CH}$ (64.5 Hz) and $J_{AA'}$ ($= J_{BB'}$) = −1.8 Hz. The appearance of the calculated spectrum is not sensitive to the magnitude of the last parameter.

1-*tert*-Butylacenaphthene.—The benzylic protons of *tert*-butylacenaphthene gave rise to a degenerate five-line pattern at 100 MHz, but, at 220 MHz, a well-resolved ABC spectrum[14a] which was analyzed with the aid of the LAOCN3 iterative program to give the parameters shown in Table I, entry 2.

1-Methylacenaphthene.—As the parameters of interest are the chemical shifts and coupling constants in the three-spin system at C-1 and C-2 (H_A, H_B, and H_C in Table I), an attempt was made to simplify the 100-MHz nmr spectrum of 1-methylacenaphthene by decoupling both the methyl and aromatic protons. Unfortunately, at power levels required to decouple the methyl group, the portion of the spectrum of interest to us became distorted, while the portion of the spectrum comprising the six-spin system (H_A, H_B, H_C, and the methyl group), after the successful decoupling of aromatic protons, could not be analyzed because we were unable to obtain satisfactory initial parameters for the iterative stage. As homonuclear spin decoupling was not possible at 220 MHz, a specimen of 1-methyl-3,5,6,8-tetradeuterioacenaphthene was prepared (see Experimental Section), whose 220-MHz spectrum (Figure 2) was sufficiently simple to permit us to deduce trial parameters for analysis by means of the LAOCN3 procedure.[14b] Satisfactory analyses of both 220- and 100-MHz spectra were achieved, although the accuracy is rather poorer than usual owing to the large number of coincident transitions and imperfect resolution. The data for long-range interactions involving the methyl group are therefore of doubtful significance.

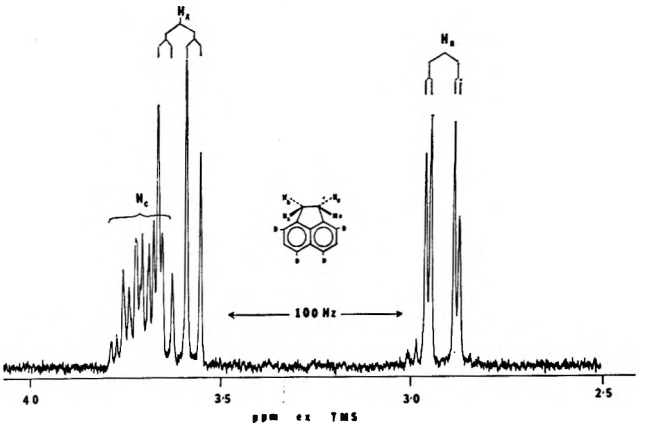


Figure 2.—Portion of 220-MHz spectrum of 1-methyl-3,5,6,8-tetradeuterioacenaphthene.

Hexachlorobicyclo[2.2.1]heptene.—The 100-MHz nmr spectrum of hexachlorobicyclo[2.2.1]heptene as approximately 10% w/v solution in CS_2 gave an AA'BB' pattern with 24 clearly identifiable lines which was analyzed iteratively by LAOCN3 procedure to give the parameters listed under entry 1, Table II. The probable errors were all less than 0.02 Hz and the largest deviation between the experimental and calculated position of any single line was 0.106 Hz. The assignment of the upfield portion of the AA'BB' multiplet to the endo protons and the downfield portion to the exo protons was arrived at on the following grounds. It has been established[15,16] that in bicyclo[2.2.1]heptenes $J_{exo,exo}$ is somewhat larger than $J_{endo,endo}$ and, as $J_{AA'}$ and $J_{BB'}$ were available from the tightly coupled spectrum and differed significantly (9.16 and 9.73 Hz, respectively), a clear choice could be made. Secondly, comparison of the differences in the chemical shifts between H_C and the parent compound in hexachlorobicyclo[2.2.1]heptenes (Table II) with the corresponding values for acenaphthenes (Table I) gave comparable values with the assignment chosen but some larger discrepancies for the alternative assignment. Finally, in norbornene[16] the resonances assigned to the analogous endo protons at C-5 and C-6 occur upfield of those assigned to the corresponding exo protons.

(12) A. A. Bothner-By and S. Castellano, *J. Chem. Phys.*, **41**, 3863 (1964), and private communication from the authors.

(13) F. S. Mortimer, *J. Mol. Spectrosc.*, **5**, 199 (1960).

(14) (a) Shown in microfilm edition. (b) A summary is given in the microfilm edition. See paragraph at end of paper regarding supplementary material.

(15) F. A. L. Anet, H. H. Lee, and J. L. Sudmeier, *J. Amer. Chem. Soc.*, **89**, 4431 (1967), and references cited therein.

(16) A. P. Marchand and J. E. Rose, *ibid.*, **90**, 3724 (1968).

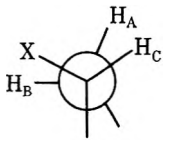
Ethylene Oxide and 1,1-Dichlorocyclopropane.—The nmr spectrum of ethylene oxide has been previously analyzed by the ^{13}C satellite method[13] as a neat liquid to give values (J_{cis} = 4.45 ± 0.1 and J_{trans} = 3.1 ± 0.1 Hz) almost identical with our results for CS_2 solution (entry 1, Table III) obtained by the iterative procedure.[12] The insensitivity of this spectrum to the magnitude of J_{gem} is reflected in the large probable error (±1.6 Hz) for this parameter in the final iteration where the root mean square (rms) error was 0.023 Hz and the largest deviation between the experimental and calculated line positions was 0.05 Hz.

The nmr spectrum of 1,1-dichlorocyclopropane in benzene has been analyzed by the ^{13}C satellite method.[17] Our results for CS_2 solution (entry 1, Table IV) are comparable. Owing to the relatively good quality of the satellite spectrum[18] and excellent convergence on iteration (rms error 0.013 Hz, largest deviation between the experimental and calculated line position 0.036 Hz), reliable results for all parameters, including J_{gem}, were obtained.

Dibenzobicyclo[2.2.2]octadiene gave a poor-quality ^{13}C satellite spectrum of the bridge protons after decoupling of the benzylic (bridgehead) protons.[19] Analysis by the method of Mortimer[13] was performed as for acenaphthene, using averages from eight spectra for the spacing assigned to the sum and difference, respectively, of the vicinal couplings.

B. Assignment of Resonances and Discussion of Geometry.—The resonances of the geminal protons at C-2 in 1-substituted acenaphthenes were assigned on the basis of the Karplus relation;[8] *i.e.*, it was assumed, following previous workers,[2-7] that in system **1** $J_{cis} > J_{trans}$. The same considerations were used to assign the coupling constants in the satellite analyses of the unsubstituted compounds (entries 1, Tables I–V).

No low-temperature neutron diffraction data on 1-monosubstituted acenaphthenes (**8**) are available and hence the central question of the exact stereochemistry of the system **1** in acenaphthene cannot be unequivocally answered. From the point of view of the present investigation, the most relevant distortions from the idealized stereochemistry of the system **1**, in which H_A is completely eclipsed by H_C and H_B is completely eclipsed by X, involve torsional changes about the C-1–C-2 bond. These are most likely to be of two kinds, represented by projections **9** and **10**. We consider that the



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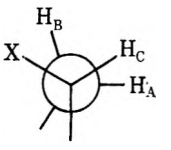


10

most instructive of the available X-ray diffraction data on acenaphthenes[20-23] are those for *cis*-acenaphthene-1,2-diol,[21] which show that the analogous distortion from perfect eclipsing owing to the nonbonded interaction between the cis vicinal oxygen atoms is of the order of 10°. Consideration of van der Waals radii suggest that in the series of 1-substituted acenaphthenes examined here the most important nonbonded interactions, *i.e.*, those between H_B and X, are likely to be *less* severe (except possibly in cases 2, 15, and 16, Table I), and hence should result in distortions smaller than *ca.* 10°.

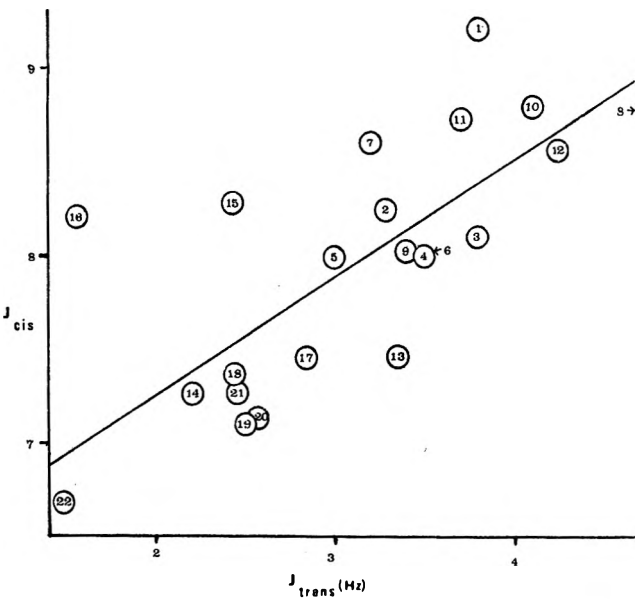


Figure 3.—Plot of $J_{vicinal,cis}$ (J_{AC}) *vs.* $J_{vicinal,trans}$ (J_{BC}) in 1-substituted acenaphthenes (**8**). Identification numbers refer to Table I. The straight line of best fit was obtained by the standard procedure and has slope 0.63, intercept on the y axis 6.00, and correlation coefficient 0.68.

Assuming, as is generally done,[8] that the most important factor determining the magnitude of vicinal coupling constants is the dihedral angle, one concludes that J_{trans} (*i.e.*, J_{BC}) in **8** should be more sensitive to distortions from perfect eclipsing than J_{cis} (*i.e.*, J_{AC}) because of the shape of the Karplus function.[8] The plot of J_{AC} *vs.* J_{BC} (Figure 3) shows considerable scatter, but there seems no unequivocal correlation between the bulk of substituent X and the deviation from the straight line of best fit, with the possible exception of 1-trimethylammonioacenaphthene (entry 16), thus suggesting that distortions are moderate.

It is apparent from the projections **9** and **10** that while distortion from perfect eclipsing must cause a decrease in J_{cis} it could be accompanied by either an increase (projection **9**) or a decrease (projection **10**) in J_{trans}. Comparison of pairs of entries in Table I where the substituents have similar electronegativity (see below) but differ in bulk leads to some very tentative suggestions. Thus the somewhat greater J_{trans} for X = Cl than for X = Br (in spite of an increase in electronegativity) suggests that the distortion (if any) is in the direction of projection **9**. On the other hand, entries 2 and 3 in Table I suggest that the *tert*-butyl group causes a distortion toward the projection **10**.

In summary, there is no evidence for *gross* distortions in monosubstituted acenaphthenes, but steric factors cannot be ignored.

C. Substituent Effects on Coupling Constants.—Previous workers[2-6,8,10c] have investigated the effect

(17) D. J. Patel, M. E. H. Howden, and J. D. Roberts, *J. Amer. Chem. Soc.*, **85**, 3218 (1963).
(18) Shown in microfilm edition.
(19) See microfilm edition.
(20) H. W. W. Ehrlich, *Acta Crystallogr.*, **10**, 699 (1957).
(21) J. Trotter and T. C. W. Mak, *ibid.*, **16**, 1032 (1963).
(22) V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).
(23) (a) R. L. Avoyan and Yu. T. Struchkov, *Zh. Strukt. Khim.*, **2**, 719 (1961); (b) *ibid.*, **4**, 631 (1963); (c) *ibid.*, **3**, 605 (1962); (d) T. C. W. Mak and J. Trotter, *Acta Crystallogr.*, **16**, 811 (1963).

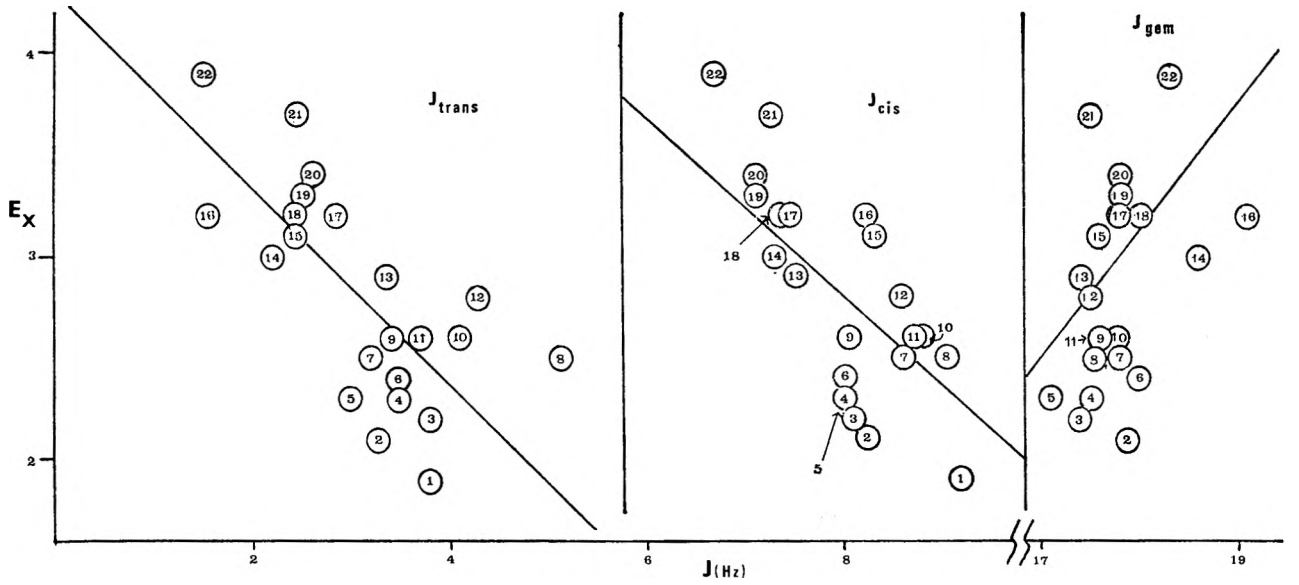


Figure 4.—Plot of coupling constants in 1-substituted acenaphthenes (8) *vs.* electronegativity of the substituents. Identification numbers refer to Table I. The straight lines of best fits were obtained by the standard procedure and have the following parameters: slope −0.48, −0.44, +0.42; intercept on the y axis 4.29, 6.32, −4.63; correlation coefficient −0.71, −0.74, 0.39 for J_{trans}, J_{cis}, and J_{gem}, respectively.

TABLE VII

LINEAR CORRELATION OF NMR PARAMETERS WITH ELECTRONEGATIVITY

System	Parameter	$\lvert J_{gem}\rvert$	J_{cis}	J_{trans}	$J_{cis} + J_{trans}$	$\delta_C - \delta_A$	$\delta_C - \delta_B$
Acenaphthene	No. of points	21	22	22	22	21	21
(Table I)	Slope	0.42	−0.44	−0.48	−0.31	0.59	0.53
	Intercept	−4.63	6.32	4.29	6.2	2.13	2.03
	Correlation coefficient	0.39	−0.72	−0.71	−0.79	0.93	0.91
Bicycloheptene	No. of points	8	8	8	8	8	8
(Table II)	Slope	1.51	−0.71	−0.49	−0.37	0.72	0.56
	Intercept	−16.3	8.9	4.7	7.3	2.0	1.8
	Correlation coefficient	0.83	−0.95	−0.84	−0.92	0.99	0.98
Oxirane	No. of points	8	9	9	9	9	9
(Table III)	Slope	−0.55	−0.40	−0.81	−0.35	0.50	0.50
	Intercept	5.8	4.3	4.5	4.9	2.3	2.2
	Correlation coefficient	−0.68	−0.67	−0.87	−0.82	0.88	0.83
Dichlorocyclo-	No. of points	7	7	7	7	7	7
propane	Slope	0.41	−0.40	−0.39	−0.26	0.55	0.57
(Table IV)	Intercept	−0.2	6.7	5.6	7.2	2.2	2.1
	Correlation coefficient	0.97	−0.94	−0.86	−0.94	0.98	0.98
Dibenzobicyclo-	No. of points	6	7	7	7	7	7
octadiene	Slope	0.11	−0.60	−0.17	−0.17	0.58	0.49
(Table V)	Intercept	1.8	8.8	3.7	5.3	2.1	2.0
	Correlation coefficient	−0.2	−0.76	−0.28	−0.56	0.96	0.95
Cyclopropane	No. of points	9	9	9	9	9	9
(Table VI)	Slope	0.32	−0.57	−0.56	−0.25	0.48	0.46
	Intercept	1.3	7.1	5.1	5.8	2.13	2.11
	Correlation coefficient	0.71	−0.99	−0.94	−0.95	0.97	0.97

of electronegativity on vicinal and geminal coupling constants in many systems and found definite correlations. Plotting the relevant data from Table I against the mean of Dailey[9] and Muller[24] electronegativities (Figure 4) confirms the general *trends* noted previously, but clearly it is futile to propose any definite correlations in view of the degree of scatter.

Besides the apparent lack of a simple relation between electronegativity and coupling constants shown in Figure 4, a number of significant particular exceptions to any proposed relation of type $J = EA + B$, where A and B are constants, can be seen in Tables I–VI. Thus the vicinal coupling constants in 1-cyanoacenaphthene (entry 8, Table I) are abnormally large, although this is not observed in the cyano derivatives of hexachlorobicyclo[2.2.1]heptene (entry 8, Table II),

(24) J. C. Muller, *Bull. Soc. Chim. Fr.*, 1815 (1964).

TABLE VIII
DIRECT COMPARISON BETWEEN COUPLING CONSTANTS

System	Parameter	$\lvert J_{gem}\rvert$	J_{cis}	J_{trans}	$J_{cis} + J_{trans}$
Bicycloheptene *vs.* acenaphthene	No. of points	7	8	8	8
	Slope	1.22	0.70	1.23	0.88
	Intercept	1.99	2.2	−1.04	1.8
	Correlation coefficient	0.54	0.97	0.93	0.98
Oxirane *vs.* acenaphthene	No. of points	6	7	7	7
	Slope	0.0	0.72	1.05	1.01
	Intercept	17.6	5.6	1.33	5.97
	Correlation coefficient	−0.04	0.90	0.73	0.90
Dichlorocyclopropane *vs.* acenaphthene	No. of points	5	6	6	6
	Slope		0.63	0.52	0.68
	Intercept		1.9	−0.40	0.00
	Correlation coefficient		0.95	0.84	0.93
Dibenzobicyclooctadiene *vs.* acenaphthene	No. of points	5	6	6	6
	Slope		0.42	−0.20	0.34
	Intercept		3.87	3.45	6.65
	Correlation coefficient		0.91	−0.32	0.55
Cyclopropane *vs.* acenaphthene	No. of points	7	8	8	8
	Slope	0.58	0.75	0.86	1.01
	Intercept	14.8	2.39	−0.30	0.10
	Correlation coefficient	0.88	0.97	0.84	0.91
Cycloheptene *vs.* cyclopropane	No. of points	6	6	6	6
	Slope	1.94	1.21	1.00	1.24
	Intercept	−19.6	−2.7	0.66	−3.05
	Correlation coefficient	0.89	0.95	0.90	0.98
Cycloheptene *vs.* oxirane	No. of points	5	6	6	6
	Slope		0.23	0.56	1.20
	Intercept		1.76	0.01	−8.8
	Correlation coefficient		0.74	0.62	0.98

ethylene oxide (entry 8, Table III), or cyclopropane (entry 8, Table VI).[25] Geminal coupling constants for all bromo derivatives (entries 14 in Tables I, IV, and VI) are too small (large negative values) and several other prominent irregularities of the same type can be discerned in Tables I–VI.

Replotting data from Tables I–VI in the manner shown in Figure 4 shows (Table VII) that the degree of correlation varies significantly but, owing to the small number of derivatives in several series, it is difficult to draw any firm conclusions. There does not appear to be any clear relation between the size of X and deviation from straight-line relationships, and hence steric factors are unlikely to be solely responsible for the poor and variable correlation between E_X and coupling constants in system 1.

We conclude that, within the comparatively narrow range of electronegativity values associated with commonly encountered functional groups, correlations between vicinal and geminal coupling constants and electronegativities of functional groups are of doubtful significance. It can be seen (Figure 4) that the scatter for J_{trans} is not much greater than that for J_{cis} and, by arguments advanced above, this confirms that the poor correlation with electronegativity is not solely due to steric factors. It is more likely that the "Dailey-type" measures of electronegativity[10d] are not very meaningful for narrow ranges found among common functional groups. In view of this and the uncertain status[26] of the underlying theory, we feel that, for the purpose of structural determination, it would be more useful to look for regularities in the influence of substituents on the magnitude of coupling constants rather than for the influence of a general property of substituents, such as electronegativity.

Comparisons of data for different systems (Tables I–VI) suggests that in the generalized system 1 substituents are indeed associated with characteristic values of vicinal coupling constants. Thus plots of the sums[27] of vicinal coupling constants in acenaphthenes *vs.* hexachlorobicyclo[2.2.1]heptenes (Figure 5) and cyclopropanes (Figure 6) appear to be straight lines.

Clearly the data in Tables I–VI could give rise to a very large number of plots of the type shown in Figures 5 and 6. These were chosen as illustrations because of the relatively large number of data available. While other plots appear less convincing, they show considerably more correlation between the substituent effects in different systems than between the sums of vicinal coupling constants and "electronegativity" in each system (Tables VII and VIII). The existence of sub-

(25) We are excluding the entry for methylcyclopropane[11] (entry 3, Table VI) because of the unlikely value quoted for J_{gem} and lack of published details concerning the analysis of the nmr spectrum.

(26) T. Schaefer and H. M. Hutton, *Can. J. Chem.*, **46**, 3153 (1967).

(27) The sums of the vicinal coupling constants were chosen because they are least susceptible to errors in analyses.

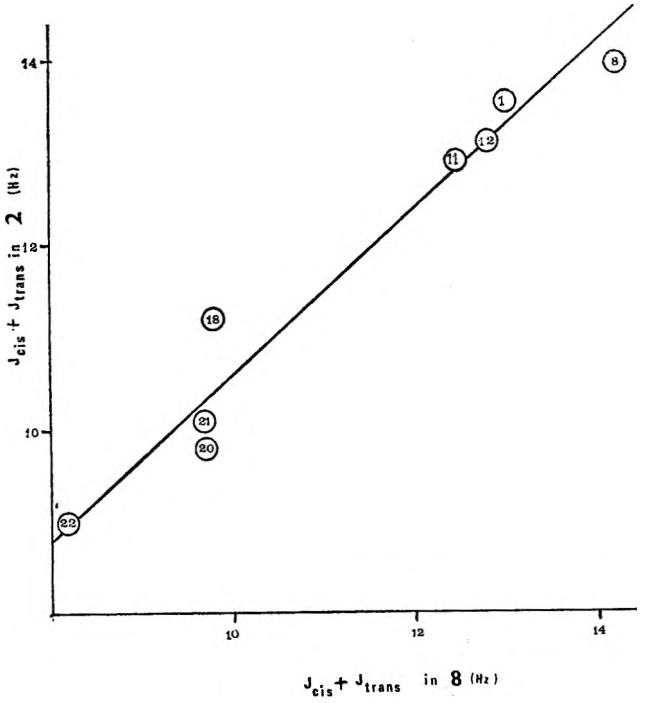


Figure 5.—Plot of the sums of vicinal coupling constants in monosubstituted hexachlorobicyclo[2.2.1]heptenes (2) *vs.* the sums of vicinal coupling constants in 1-substituted acenaphthenes (8). Identification numbers refer to Tables I and II. The straight line of best fit was obtained by the standard procedure and has slope 0.88, intercept on the y axis 1.8, and correlation coefficient 0.98.

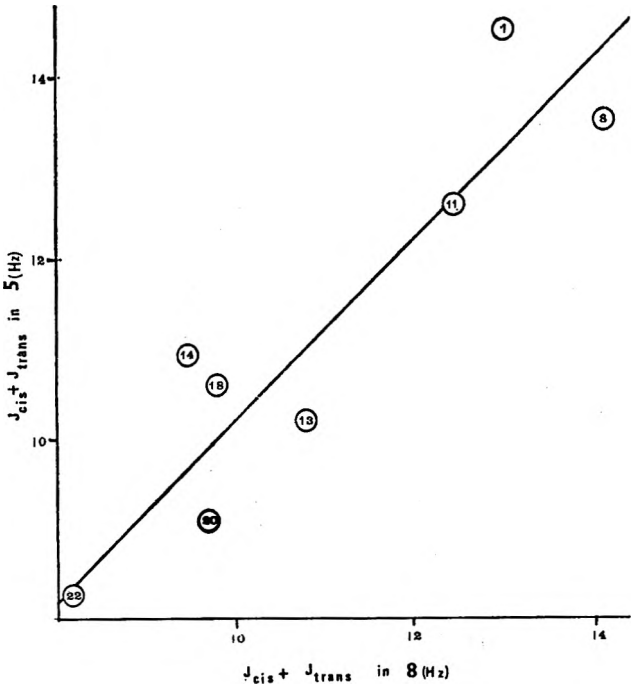


Figure 6.—Plot of the sums of vicinal coupling constants in monosubstituted cyclopropanes (5) *vs.* the sums of vicinal coupling constants in 1-substituted acenaphthenes (8). Identification numbers refer to Tables I and VI. The straight line of best fit was obtained by standard procedure and has slope 1.01, intercept on the y axis −0.10, and correlation coefficient 0.91.

stituent effects of this type has obvious predictive value for structural work.

D. Substituent Effects on Chemical Shifts.—The causes of some substituent effects on chemical shifts in system 1 will be discussed below; in this section we are concerned with establishing the *regularity*, if any, in substituent influences in this system for the purpose of obtaining correlations useful in structural determination.

It is well known[28] that the minimum experimental conditions for obtaining genuinely meaningful chemical shift data consist of extrapolation to infinite dilution in a completely inert, isotropic solvent using suitable internal standards. Such conditions must conflict with even the most painstaking routine operations because spectral analysis on very dilute solutions becomes virtually impossible, owing to unfavorable signal to noise ratio, and because the solubility of the majority of organic compounds in "inert isotropic solvents" is inadequate.[29] As the principal purpose of this work was to establish correlations usable in structural determinations, the nmr spectra of the series of 1-substituted acenaphthenes 8 were determined in deuteriochloroform solutions. For a number of compounds (Table I) it was also possible to obtain spectra for dilute (1–3%) solutions in carbon tetrachloride. It can be seen that, although the actual chemical shifts in the two solvent systems vary quite appreciably (up to 0.13 ppm), the internal chemical shifts vary considerably less and it is the latter which are most likely to be useful in the present context.

Several investigators[2-6] have commented about the good correlation between electronegativity and the internal chemical shifts in systems incorporating the fragment 1, and analogous plots for 1-substituted acenaphthenes (Figure 7) are indeed straight lines. This indicates that solvent effects are unlikely to be a major influence.[32] We consider, however, that plots of this nature are of little direct significance to the problem of the relation between shielding and electronegativity in complex molecules, because the electronegativity values of "Dailey type" [9,24] are linear functions of analogous internal chemical shifts in the corresponding ethyl derivatives CH_3CH_2X. In other words, plots of the type shown in Figure 7 are plots of $\delta_{H_\alpha} - \delta_{H_\beta}$ in two systems $CH_\beta CH_\alpha X$ differing only in stereochemistry.

Data in Tables I–VI reveal that all substituents, with the exception of $-SiMe_3$ in all systems[33] investigated here, deshield the geminal proton (H_C) and the trans vicinal proton (H_A) with respect to the parent compound (X = H), but the eclipsed cis vicinal proton (H_B) generally experiences smaller relative downfield shifts and in several cases is actually shielded. Not surprisingly, with most substituents the eclipsed vicinal proton appears upfield of the trans vicinal proton, *i.e.*, the values in the column $\delta_A - \delta_B$ are generally positive. Carbonyl derivatives (X = COOH, –COOMe, –CO-

(28) P. Laszlo in "Progress in NMR Spectroscopy," Vol. 3, Pergamon Press, Elmsford, N. Y., 1967, Chapter 6.

(29) It has been shown recently[30] that even carbon tetrachloride, which has been almost universally used as an "inert isotropic solvent" in nmr spectroscopy, is not always reliable, while the ubiquitous deuteriochloroform is known[31] to cause quite large solvent shifts.

(30) T. Schaefer, B. Richardson, and R. Schwenk, *Can. J. Chem.*, **46**, 2775 (1968).

(31) P. Laszlo, *Bull. Soc. Chim. Fr.*, 2658 (1964).

(32) R. F. Zürcher in "Progress in NMR Spectroscopy," Vol. 2, Pergamon Press, Elmsford, N. Y., 1967, Chapter 5.

(33) Data for hexachlorobicyclo[2.2.1]heptenes (Table II) can be compared with those for the remaining systems only after correcting for the inherent differences in chemical shifts between H_A and H_B (0.49 ppm), which involves making the unverifiable assumption that this factor remains constant throughout the series.

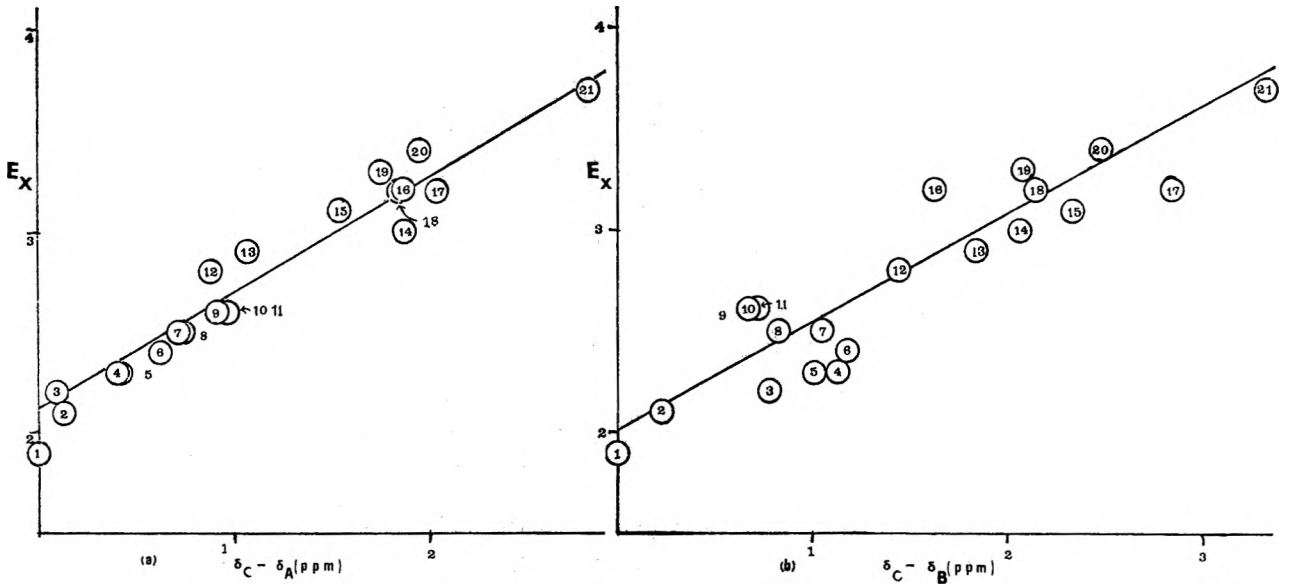


Figure 7.—Plots of the internal chemical shifts in 1-substituted acenaphthenes (**8**) *vs.* electronegativity of the substituent: (a) for the proton trans to the substituent (H_A); (b) for the proton cis to the substituent (H_B). Identification numbers refer to Table I. The straight lines of best fit were obtained by standard procedure and have the following parameters: slope 0.59, 0.53; intercept on y axis 2.13, 2.03; correlation coefficient, 0.93, 0.91 for plots 10a and 10b, respectively.

NH_2, –COMe, and –CHO) show either the opposite or erratic behavior, which can be readily rationalized by taking into account the variable conformation of the highly anisotropic carbonyl group. In the acenaphthene series (Table I, entry 16) but not in the dibenzobicyclo[2.2.2]octadiene series (Table V, entry 16), the trimethylammonium group also gives a negative value for $\delta_A - \delta_B$.

Clearly caution is necessary in utilizing the "eclipsed upfield" rule, particularly where the substituent lacks axial symmetry about the C–X bond, but it is capable of giving structural information.[10a,34] The effect of the methyl group has been established independently.[35]

Comparing the values of $\delta_A - \delta_B$ in Tables I–VI for substituents where conformational factors can be neglected (*i.e.*, here for X = Me, *tert*-butyl, CN, Br, Cl, and F) shows that the magnitude of the effect varies considerably without showing any obvious trends for the limited data available. It is therefore important that for structural determinations, an appropriate model should be chosen.

E. Rationalization of Some Substituent Effects in Fragment 1.—Because of the inherent difficulties in theoretically estimating chemical shifts, the main aim of this work has been to provide empirical parameters for common substituent effects which may be transferred from one system to another. However, a number of insights into the factors which contribute to substituent-induced chemical shifts may be gained from a collection of selected data from Tables I–VI. For ease of interpretation, the substituents to be examined have been restricted to substituents where the X in the C–X bond is a first-row element. In addition highly anisotropic groups such as carbonyl containing substituents have been given minimal consideration. Even with these limitations, no general, highly accurate correlations can be made which can account for all of the observed chemical shifts. Thus the estimation of substituent chemical shifts must remain empirically based. However, within the limitations specified by the selection of data, some trends are detected which may prove generally useful and should serve as the basis for future investigations.

The possible contributing factors which generate substituent chemical shifts have been discussed in detail by many authors.[10e,32] The diamagnetic screening term is the dominant effect on proton chemical shifts and it is directly proportional to the electron density at the proton in question. While this fact has been recognized for many years, the analysis of the electron density changes in terms of the various contributing factors (inductive effect, electric field effects, etc.) has remained uncertain. When chemical shift variations in substituted alkanes of 0.3 ppm or less are being considered, any or all of the possible contributors (diamagnetic shielding, short-range paramagnetic interaction, neighboring group anisotropy, solvent effects, and intermolecular interactions) may provide a rationalization. Larger changes can only be accounted for by the diamagnetic screening term or less commonly by the neighbor anisotropy term when a highly anisotropic group is involved.

The most readily apparent chemical shift change with substitution occurs at the geminal (α) proton. Many authors have provided electronegativity correlations to account for this behavior, but deviations from these simple correlations are well known. The definitive studies by Cavanaugh and Dailey[9] and Spiesecke and Schneider[36] provided a basis for subsequent studies.

The X substituents for system **1** can be arranged in order of increasing downfield shift and this ordering correlates moderately well with the electronegativity of X (of Tables I–VI and Figure 7). There are a few *minor* inversions from substrate to substrate, but these are found with groups which have large magnetic anisotropies (*e.g.*, C=O) or the substituent to carbon

(34) C. J. Moye and S. Sternhell, *Aust. J. Chem.*, **19**, 2107 (1966); R. H. Andreatta, V. Nair, and A. V. Robertson, *ibid.*, **20**, 2701 (1967).

(35) E. Pretsch and W. Simon, *Helv. Chim. Acta*, **52**, 2133 (1969).

(36) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 722 (1961).

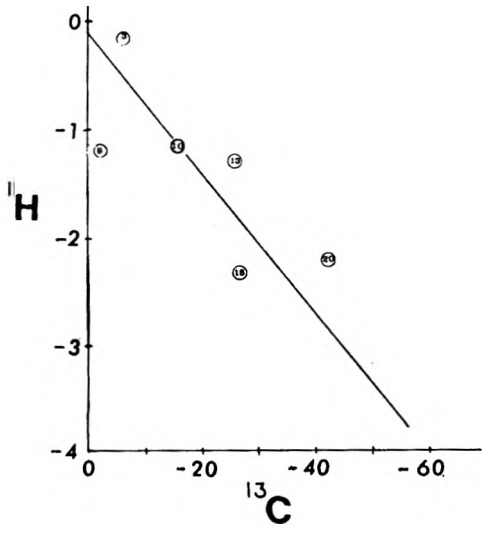


Figure 8.—Plot of α-proton shift of substituted acenaphthenes *vs.* ^{13}C substituent effect (from ref 38). Similar plots are obtained for methyl, ethyl, and cyclopropyl derivatives (see Table X). Substituents are labeled according to Table I.

bond involves a non-first-row element (*e.g.*, Br·). This substituent sequence holds not only for systems 2–8 but also for methyl, ethyl,[10] adamantyl,[37] and vinyl compounds.[10] Furthermore it correlates well with the ^{13}C chemical shifts of the carbons in the C–X group of simple alkanes.[38]

In addition to the substituent dependence, a careful examination reveals that the influence of a given substituent depends on the substrate in question. This dependence is illustrated by the substituent chemical shifts of protons α to an OH (relative to the corresponding hydrocarbon): methyl (3.16), cyclopropyl (3.15), ethyl (2.73), isopropyl (2.61), system **7** (2.26), system **8** (2.23), system **2** (2.14), 2-adamantyl (2.02), vinyl (1.22). A similar order of substrates is shown with other electronegative substituents.

The substrate dependence can be put on a quantitative basis by plotting the α-proton shift against a standard ^{13}C substituent chemical shift (Figure 8). Although this plot is clearly not a linear function—proton shifts change more slowly than carbon shifts—a least squares treatment can be used to provide an approximate measure of substrate sensitivity. The available results are given in Table IX. There is insufficient data for other substrates to provide a meaningful plot. The cyano group invariably falls off the correlation line and this can be attributed to a low value for the carbon shift of the carbon α to cyano. The apparently anomalous position of the acenaphthyl substrate is readily understood when it is realized that the data for fluoride as a substituent were not available. Thus the approximation of a curved line by a straight line will fail. This emphasizes the need for a wide range of data if a measurement of substrate sensitivity is to be made. A knowledge of substrate sensitivity will be useful for chemical shift predictions because a relationship akin to the classical Hammett $\sigma\rho$ treatment can be applied. Because of the limitations set by compound and data availability, the following relationship (eq 1) is suggested for chemical shift estimation,

$$\Delta\delta_{RX} = \Delta\delta_{EtX};\ \Delta\delta_{ROH}/\Delta\delta_{EtOH} \quad (1)$$

where $\Delta\delta$ represents the substituent chemical shift of the α proton relative to the corresponding hydrocarbon RH. Of course other common substituents besides OH could be used, provided that the magnitude of $\Delta\delta$ is large enough to provide a reliable ratio. If a sufficiently wide range of substituents is available, it would be preferable to use an analysis based on Table IX. The results for estimating acenaphthene shifts with the equation above are shown in Table X. It is clear that

Table IX

Substrate Sensitivity to Substituent[a] (Correlation of Proton Chemical Shifts with Carbon Chemical Shifts)

Substituent	Slope (m)	Intercept (c)	Correlation coefficient
Cyclopropyl	0.060	−0.58	0.94
Methyl	0.054	−0.90	0.92
Ethyl	0.049	−0.75	0.90
Acenaphthenyl[b]	0.065	−0.10	0.86
Vinyl	0.019	−0.30	0.82

[a] Data for plot of substituent-induced α-proton shift (δ_H) against ^{13}C substituent shift (δ^{13}_{CX}). $\delta_H = m\,\delta^{13}_{CX} + c$. Note that the ^{13}C data is for simple alkanes from ref 38. [b] This correlation does not include the fluoro derivative; see text.

Table X

Comparison of Observed[a] and Predicted Chemical Shifts of Acenaphthene Derivatives Based on Equation 1

X	Calcd	Obsd	Calcd − obsd
Me	−0.04	−0.17	0.13
CH_2COMe	−0.55	−0.71	0.16
CH_2COOH	−0.65	−0.75	0.10
CN	−1.17	−1.19	0.02
$CONH_2$	−1.08	−1.03	−0.05
COOMe	−1.12	−1.13	0.01
COOH	−1.18	−1.19	0.01
Ph	−1.39	−1.35	−0.04
NH_2	−1.48	−1.35	−0.13
Br	−1.98	−2.35	0.37
$NHCOCH_3$	−1.85	−2.56	0.71
Cl	−2.06	−2.31	0.25
OMe	−1.98	−2.03	0.05
OH	−2.15	−2.23	0.08
OCOMe	−2.51	−3.14	0.63
F	−2.76		

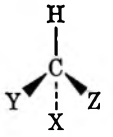
[a] The values for EtOH and EtX are taken from ref 10.

major discrepancies arise with the highly anisotropic *N*-acetyl and *O*-acetyl substituents and this serves as a warning that highly anisotropic groups should be treated with caution.

The combination of substituent and substrate dependence of chemical shifts of α protons clearly supports the long-held view that the diamagnetic screening term is dominant in controlling proton chemical shifts. In particular the magnetic anisotropy of the C–X bond cannot contribute significantly to the observed α-proton shift. This term should be essentially independent of substrate given the limited geometry available for an H–C–X group. Only a change in H–C–X bond angle should alter this term significantly and there is no correlation between bond angle and substrate sensitivity. The results for the methyl and cyclopropyl

(37) R. C. Fort and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 789 (1965).
(38) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley, New York, N. Y., 1972, pp 47, 48.

compounds are particularly informative here, because these groups of compounds should show the largest variation in bond angle, but their sensitivities to a given substituent are very similar. In addition, the close correlation between proton and carbon shifts further supports this conclusion because the magnetic anisotropy contribution would be expected to be substantially different for carbon and hydrogen. Their geometric orientation with respect to the anisotropic group and the substantial difference in their gyromagnetic ratios should lead to quite different anisotropy contributions.



The ordering of substrates is readily explicable in terms of an inductive effect model. Consider the molecular fragment shown in the structure, where X is an electronegative substituent which withdraws electrons from carbon (relative to H as a substituent). The carbon in turn withdraws electrons from the C–H, C–Y, and C–Z bonds. If one of the substituents Y or Z is a more electron-rich element or has a more polarizable bond (*i.e.*, any of the substrates studied here), then the inductive effect of the X group will be compensated predominantly by the C–Y group rather than the C–H group. Thus, of all the substrates available, the methyl group should show greatest substituent sensitivity. In the other systems, Y and Z are carbon atoms and the substrate sensitivity reflects the ability of the carbon framework to replace the electrons withdrawn by X. The more readily the carbon framework can provide electrons the less demand there is on hydrogen and so the lower the substrate sensitivity. In the strained cyclopropyl system, inductive electron withdrawal by X would weaken the C–C bonds, a highly unfavorable process, and thus major compensation is provided by the C–H bond and a large substrate sensitivity results. Simple alkyl compounds show a lower sensitivity, followed by the electron-rich systems **2**, **7**, and **8** and finally the readily polarizable vinyl group. The position of the adamantyl group as a low-sensitivity framework is interesting and suggests the intriguing possibility that the number of β carbon–carbon bonds is an important factor in governing substrate sensitivity. This is consistent with the inductive model, as β carbon–carbon bonds will be better able to compensate for electron removal from the β carbon than β carbon–hydrogen bonds.

The interpretation of the vicinal (β) hydrogen shifts H_A and H_B is complex. The magnitude of the observed shifts is sufficiently small that any or all of the factors which control chemical shifts could make a significant contribution. In a rigid system, the different orientation of H_A and H_B to the substituent X provides a limited probe for separation of these contributions. Zürcher[32] has given a thorough review of the necessary relationships. Since the shift of the α proton (H_C) is dominated by the inductive effect, a plot of H_C *vs.* H_A or H_B should show the importance of inductive effects. Using all the acenaphthene data, a mild trend of H_A to follow H_C was shown (correlation coefficient 0.69) and the eclipsed proton H_B showed no correlation. Thus the inductive effect does not dominate β-proton shifts. Some of the data spread may be attributed to the effect of anisotropic groups of unknown conformation. However, even when the data is limited to axially symmetrical substituents no general trends were apparent. An attempt was made to predict some of these shifts using Zürcher's parameters[32] for electric field and anisotropy contributions, but this also failed (Table XI).

In an attempt to overcome some of the deficiencies of the point dipole approximation an alternative representation was tried. The C–X bond electric field was approximated by point charges at the nuclei and a Buckingham[39] electric field calculation was performed. The magnitudes of the nuclear charges were chosen so as to reproduce the dipole moment in conjunction with the C–X bond length. The resultant electric field was calculated at the center of the C–H bond in question. The chemical shifts calculated by this method were usually within about 0.1 ppm of the simple point dipole values and so offer no advantages.

Thus there is no simple single correlation which will account for β-proton shifts. However, it is apparent that for simple substituents (Me, NH_2, OH, F), the electrical character of the X substituent does have a marked influence on the shifts of H_A and H_B (Figure 9). The breakdown of this behavior into the contributions due to through-bond and through-space effects must await further data.

The major stumbling block in all these calculations is the upfield shift induced at the eclipsed hydrogen. As Zürcher has shown,[32] none of the normal electric field or anisotropy contributions can reproduce this behavior. Zürcher interpreted the results as a solvent effect, but this effect has since been shown to be insufficient by the work of Simon[35] among others. Since none of the recognized factors controlling chemical shift can account for the observed behavior, it seems that some previously undetected effect must be invoked.

Whatever this mechanism is, it must be strongly geometry dependent. Furthermore, it would seem from Figure 9 that the factor responsible for the upfield shift is approximately constant for each substituent. Since it is most unlikely that a completely new electromagnetic phenomenon is responsible for this behavior, it seems reasonable to suggest that a neglected component in the diamagnetic shielding term is responsible. The strong dependence on dihedral angle (0.7 ppm at 0°, 0.4 ppm at 60°, 0 at 120°) (Figure 10) and the approximate independence to the substituent are strongly reminiscent of the Karplus relationship for vicinal coupling constants.[40] This suggests that the explanation lies in a small amount of backbonding from the substituent to the eclipsed hydrogen. This will increase the electron density at the proton and generate an upfield shift. Unfortunately, no reliable data are available for a dihedral angle of 180° and so determination of the total shape of the backbonding contribution must await further experiments.

Experimental Section

Melting points were obtained on a Kofler block and are uncorrected. Ir spectra were determined with a Perkin-Elmer Model

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(40) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

TABLE XI

OBSERVED AND CALCULATED RELATIVE PROTON CHEMICAL SHIFTS OF THE RIGID SYSTEM XC–CH FOR DIFFERENT SUBSTITUENTS X AND TORSION ANGLES ϕ

System	Torsion angle ϕ	$-\Delta\delta_{obsd}$,[a] ppm	κ[b]	$\Delta\chi_1$[c]	$-\Delta\delta_{el}$, ppm	$-\Delta\delta_{magn}$, ppm	$-\Delta\delta_{calcd}$,[d] ppm	$-\Delta\delta_{obsd} - \Delta\delta_{calcd}$, ppm
				Chloro Compounds[e]				
8	0	0.16	−9.0	0	0.83	0	0.83	0.67
			−5.7[h]	−7.5	0.52	0.06	0.58	0.42
	128	0.46	−9.0	0	0.26	0	0.26	−0.20
			−5.7[h]	−7.5	0.16	0.02	0.18	−0.28
2	0	0.22	−9.0	0	0.88	0	0.88	0.66
			−9.0	−7.5	0.88	0.05	0.93	0.71
	120	0.59	−9.0	0	0.50	0	0.50	−0.09
4	0	0.26	−9.0	−7.5	0.49	−0.11	0.38	0.13
	144[o]	0.34	−9.0	−7.5	<0.22	−0.05	<0.17	−0.17
7	0	0.07	−9.0	−7.5	0.80	0.07	0.87	0.80
	120	0.72	−9.0	−7.5	0.51	0.02	0.53	−0.19
5	0	0.54	−9.0	−7.5	0.51	−0.15	0.34	0.20
			−5.7	0	0.34	0	0.34	0.20
	144	0.67	−9.0	−7.5	<0.22	0.05	<0.17	−0.49
				Bromo Compounds[f]				
8	0	0.29	−9.4[i]	−10[p]	0.84	0.08	0.92	0.63
			−6.0[j]	−10	0.53	0.08	0.61	0.32
	128	0.48	−9.4	−10	0.27	0.03	0.30	−0.18
			−6.0	−10	0.16	0.03	0.19	−0.29
3	0	0.61	−9.4	−10	0.50	−0.15	0.45	−0.17
	144	0.76	−9.4	−10	<0.25	−0.06	<0.19	−0.57
				Cyano Compounds[g]				
8	0	0.36	−14.8[p]	−30[k]	0.41	−0.19	0.22	−0.14
			−14.8	0	0.41	0	0.41	0.05
	128	0.46	−14.8	0	0.16	0	0.16	−0.30
2	0	0.15	−14.8	0	0.50	0	0.50	0.35
	120	0.21	−14.8	0	0.36	0	0.36	0.15
4	0	0.51	−14.8	−30	0.33	−0.20	0.13	−0.38
			−14.8	0	0.33	0	0.33	−0.18
	144	0.63	−14.8	0	<0.15	0	<0.15	−0.48
				Methyl Compounds				
8	0	−0.62	0	*l*	0	−0.57[n]	−0.57	0.05
				m	0	−0.37[n]	−0.37	0.25
	128	0.09	0	*l*	0	0.01	0.01	−0.08
				m	0	0.06	0.06	−0.03

[a] See Tables I–VI. [b] $\times 10^{-12}$ esu. [c] $\times 10^{-30}$ cm^3/molecule. [d] $\Delta\delta_{calcd} = \Delta\delta_{el} + \Delta\delta_{magn}$. [e] Center of dipole from carbon atom = 0.90 Å (ref 32). [f] Center of dipole from carbon atom = 0.96 Å. [g] Center of dipole from carbon atom = 2.1 Å (ref 32). [h] $A = -2.6 \times 10^{-12}$ esu and μ(C–Cl) = 2.2 D. [i] $A = -4.07 \times 10^{-12}$ esu and μ(C–Br) = 2.3 D. [j] $A = -2.6 \times 10^{-12}$ esu and μ(C–Br) = 2.3 D. [k] Mean of values determined by W. Zeil and H. Buchert, *Z. Phys. Chem.*, **38**, 47 (1963), and G. S. Reddy and J. H. Goldstein, *J. Phys. Chem.*, **39**, 3509 (1963). [l] $\Delta\chi_{C-C} = 21.33$ and $\Delta\chi_{C-H} = 12.57$. [m] $\Delta\chi_{C-C} = 13.98$ and $\Delta\chi_{C-H} = 11.00$. [n] Calculated for H–C–C and C–C–CH_3 angles of 109°. Corresponding angles in acenaphthene are 119°. [o] Reference 3. [p] Reference 32.

221 spectrophotometer. Nmr spectra were obtained on a Varian Associates Model A-60 or HA-100 spectrometer using tetramethylsilane, unless otherwise indicated, as internal reference. Some of the spectra were recorded with a Varian HR-220 spectrometer. Elemental analyses were performed by the Australian Microanalytical Service, Melbourne.

Acenaphthene was purchased from Fluka, A.G., and recrystallized from ethanol before use. Acenaphthylene was obtained from the same source, and purified by recrystallization from pentane. Diethyl ether, benzene, petroleum ether (bp 58–64°), ethyl acetate, and acetone were purified by standard procedures.

1-Acetoxy-,[41] 1-bromo-,[42-44] 1-chloro-,[45] 1-acetonyl-,[45] 1-phenyl-,[46] 1-methyl-,[46,47] and 1-methoxy acenaphthene,[48] as well as 1-acenaphthenol,[41] diethyl 1-acenaphthenylmalonate,[43] 1-acenaphthenecarbonitrile,[43,49] 1-acenaphthenecarboxylic acid,[43] 1-acenaphthenemalonic acid,[44,46] 1-acenaphtheneacetic acid,[46] ethyl 1-acenaphthenylacetoacetate,[45] trimethyl 1-acenaphthenylammonium bromide,[50] 1-acenaphthenamine,[51] *N*-(1-acenaphthenyl)acetamide,[51] hexachlorobicyclo[2.2.1]heptene,[52] 1,1-dichlorocyclopropane,[53,54] and dibenzobicyclo[2.2.2]octadiene[55,56] were prepared as previously described.

1-Acenaphthenecarboxamide.—1-Acenaphthenecarbonitrile (4.0 g) was warmed at 40–50° with 10 *M* hydrochloric acid (25 ml) for 75 min. Water (300 ml) was added to the solution and the precipitate which formed was separated by filtration and washed with ether and saturated aqueous $NaHCO_3$ solution. The crude product was recrystallized from ethyl acetate and sublimed [130–140° (0.5 mm)] to give colorless crystals of 1-ace-

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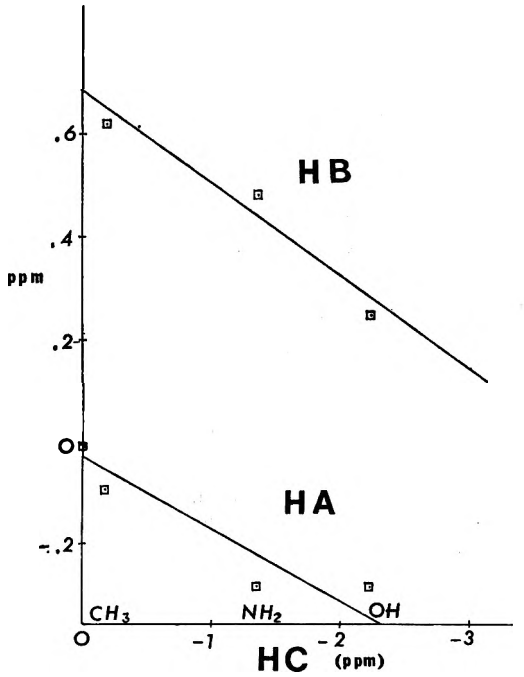

Figure 9.—Plot of H_A *vs.* H_C and H_B *vs.* H_C for substituted acenaphthenes. Similar plots are obtained for cyclopropyl derivatives.

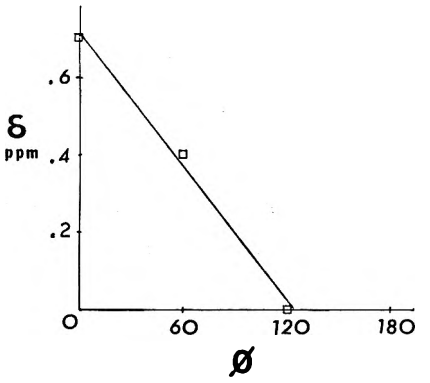

Figure 10.—Plot of backbonding contribution to β chemical shifts as a function of dihedral angle (ϕ).

naphthenecarboxamide (2.2 g, 50%): mp 217–218° (sealed tube); uv max (95% C_2H_5OH) 228 nm (ϵ 62,000), 288 (5800), 320 (800); ir ($CHCl_3$) 3520, 3409, 3005, 1680, 1580, 1368, 1052, 1028, 1010, 710 cm^{-1}; nmr ($CDCl_3$) (for signals assigned to benzylic protons, see Table I) δ 4.26 (s, 2, $CONH_2$), 7.08–7.75 (m, 6, aromatics).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.2; H, 5.65; N, 6.96.

1-*tert*-Butyl-1-acenaphthenol.—A solution of *tert*-butyllithium in ether was prepared from *tert*-butyl chloride (13.7 g), lithium shavings, and dry ether (500 ml).[57] With the temperature at −40°, acenaphthenone (6.0 g) dissolved in a minimum of dry ether was added slowly over 2 hr. The reaction mixture was stirred for a further 2 hr at the same temperature. The lithium addition compound and excess lithium were decomposed by the addition of water. The mixture was extracted with ether (2 × 75 ml) and the combined ether extracts were dried ($MgSO_4$) and concentrated. The crude product was chromatographed on neutral alumina. Benzene eluted acenaphthenone (1.0 g), ether eluted 1-acenaphthenol (1.85 g), and benzene–ether (15%) eluted the crude product (2.1 g), which was rechromatographed to give as a clear oil, 1-*tert*-butyl-1-acenaphthenol (1.6 g, 20%): $n^{25}D$ 1.688; uv max (95% C_2H_5OH) 227 nm (ϵ 73,000), 287 (6800); ir (liquid film) 3450, 3042, 2947, 1592, 1452, 1365, 1012, 817, 797, 778 cm^{-1}; nmr ($CDCl_3$) δ 0.98 [s, 9, $C(CH_3)_3$], 2.15 (s, 1, OH), 3.09 (d, 1, J = 18 Hz, CH_2), 3.79 (d, 1, J = 18 Hz, CH_2), 6.88–7.62 (m, 6, aromatics). *Anal.* Calcd for $C_{16}H_{18}O$: C, 84.9; H, 8.0. Found: C, 84.8; H, 8.0.

1-*tert*-Butylacenaphthylene.—1-*tert*-Butyl-1-acenaphthenol (0.12 g) was warmed on a steam bath for 2.5 hr with pyridine (1 ml) and thionyl chloride (0.15 g). The reaction mixture was poured into water and extracted with ether. The combined ether extracts were washed with 3 *N* sulfuric acid (2 × 20 ml), dilute sodium bicarbonate solution (20 ml), and water. The ethereal extract was dried ($MgSO_4$), concentrated, and filtered through silica gel in light petroleum to give, on evaporation of the solvent, yellow crystals of 1-*tert*-butylacenaphthylene (0.084 g, 84%): mp 38–40°; ir (liquid film) 2900, 1452, 1381, 1263, 1095, 1030, 839, 810, 771, 729, 718 cm^{-1}; nmr ($CDCl_3$) δ 1.48 [s, 9, C $(CH_3)_3$], 6.71 (s, 1, C=CH), 7.13–7.87 (m, 6, aromatics). *Anal.* Calcd for $C_{16}H_{16}$: C, 92.3; H, 7.7. Found: C, 92.2; H, 7.9.

1-*tert*-Butylacenaphthene.—A solution of 1-*tert*-butylacenaphthylene (0.10 g) in absolute ethanol was hydrogenated over Raney nickel at room temperature under 2 atm of hydrogen. The reaction mixture was filtered and the solvent was removed to give colorless crystals of 1-*tert*-butylacenaphthene (0.095 g, 95%). The compound was further purified by filtration through silica gel in light petroleum: mp 37–38°; uv max (95% C_2H_5OH) 227 nm (ϵ 76,000), 287 (6800); ir (liquid film) 3040, 2944, 2857, 1580, 1484, 1450, 1395, 1369, 1210, 832, 806, 779 cm^{-1}; nmr ($CDCl_3$) δ 0.92 [s, 9, $C(CH_3)_3$] (see Table I for benzylic protons), 6.95–7.62 (m, 6, aromatics). *Anal.* Calcd for $C_{16}H_{18}$: C, 91.4; H, 8.6. Found: C, 91.2; H, 8.9.

Methyl 1-Acenaphthenecarboxylate.—A saturated solution of diazomethane in ether (0°) was added to a mixture of 1-acenaphthenecarboxylic acid (0.5 g) in methanol (20 ml) at 0°. The reaction mixture was allowed to stand at room temperature for 30 min before the solvent was evaporated. The residue was chromatographed on silica gel in light petroleum to give a thick oil which became crystalline on standing in the refrigerator for several days. This was rechromatographed to yield colorless crystals of methyl 1-acenaphthenecarboxylate (0.4 g, 75%): mp 31–33°; uv max (95% C_2H_5OH) 227 nm (ϵ 71,000), 288 (6800); ir ($CHCl_3$) 3040, 3008, 2956, 1731, 1601, 1432, 1320, 1267, 1165, 1030, 840 cm^{-1}; nmr ($CDCl_3$) δ 3.72 (s, 3, $COOCH_3$) (for signals assigned to benzylic protons see Table I), 7.15–7.70 (m, 6, aromatics). *Anal.* Calcd for $C_{14}H_{12}O_2$: C, 79.2; H, 5.6. Found: C, 79.3; H, 5.5.

1-Methylacenaphthene-*3,5,6,8-d*$_4$.—1-Methylacenaphthene (0.5 g) was heated at reflux in deuteriotrifluoroacetic acid (7.5 ml), carbon tetrachloride (2.5 ml), and difluorophosphonic acid (0.05 ml) for 3 days. The solvent was evaporated and the crude product was chromatographed on neutral alumina to yield 1-methylacenaphthene-*3,5,6,8-d*$_4$ (0.10 g, 65%), nmr ($CDCl_3$) δ 1.33 (d, 3, CH_3) (for signals assigned to benzylic protons see Table I), 7.32 (s, 2, $H_{4,7}$).

Additional Notes.—Two papers[58,59] have appeared since this manuscript was completed which should be considered in conjunction with this work. Wiberg, *et al.*,[58] have reported detailed data for cyclopropyl derivatives which can be added to Table VI. They also note the substrate dependence of α-proton chemical shifts, and the general correlation of coupling constants with electronegativity. Their assignment of the β-proton shifts to anisotropy effects appears questionable. The discussion by Boaz[59] of chemical shifts in terms of electric dipole contributions appears to us to have more merit.

Acknowledgments.—The authors wish to thank Dr. W. Tochtermann (University of Heidelberg), Dr. L. D. Hall (University of British Columbia), and Dr. S. L. Smith (University of Kentucky) for gifts of samples and helpful correspondence. This work has been supported by funds from the Australian Research Grants Committee (Grant No. 15567 to S. S.) and a grant from Eli Lilly and Co. to J. B. G.

Registry No.—1-*tert*-butyl-1-acenaphthenol, 40748-33-2; 1-*tert*-butylacenaphthylene, 38206-03-0.

(57) P. D. Bartlett and E. B. Lefferts, *J. Amer. Chem. Soc.*, **77**, 2804 (1955).

(58) K. B. Wiberg, D. E. Barth, and P. E. Schertler, *J. Org. Chem.*, **38**, 378 (1973).

(59) H. Boaz, *Tetrahedron Lett.*, 55 (1973).

Supplementary Material Available.—A table of analysis results for 1-methylacenaphthene and three figures will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3122.

A Novel Reaction between 3,5-Dinitroacetophenone–Acetone and Secondary Amines Yielding Naphthalenic Structures

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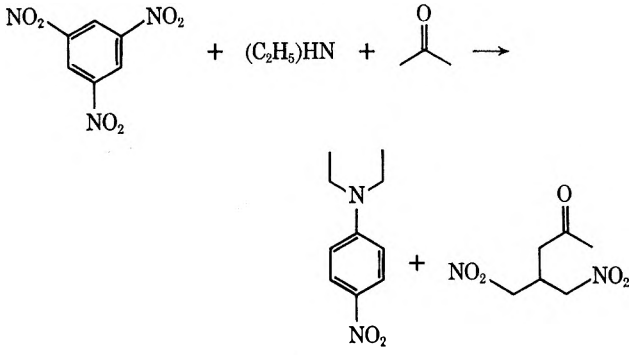
The exothermic reaction which occurs upon the addition of a secondary amine to a mixture of 3,5-dinitroacetophenone and acetone was investigated to determine the nature of the products. Instead of the expected Meisenheimer addition product, a new compound, 1-methyl-3-diethylamino-5,7-dinitronaphthalene, was formed. Employing 3,5-dinitrobenzaldehyde as the starting material resulted in the formation of the analogous 1,3-dinitro-7-diethylaminonaphthalene. The scope of the reaction is investigated.

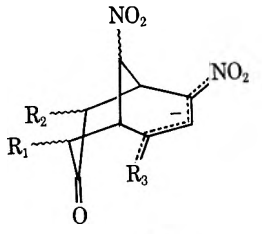
The chemistry of complexes arising from the interaction of electron-deficient aromatics with organic bases has received considerable attention during the last 10 years and has been reviewed.[1,2] These so-called Meisenheimer complexes in which the negative charge is delocalized over a pentadienide system have been observed under certain conditions to undergo an internal cyclization to form a second bond and a stable bicyclic anion. An example is the reaction between trinitrobenzene, acetone, and diethylamine.



Although, as shown above, the products usually isolated are *N*,*N*-diethyl-*p*-nitroaniline and 2-acetonyl-1,3-dinitropropane,[3] the intermediate complex Ia can be isolated under special conditions.[4] Such structures with electron-withdrawing substituents other than nitro and ketones other than acetone have been isolated (Ib, Ic).[5]

Analogous products and intermediates might be expected from the reaction of 3,5-dinitroacetophenone, acetone, and alkylamines. It was hoped to obtain some otherwise difficultly available acetophenones by means of this reaction.

In fact, when diethylamine is added to an acetone solution of 3,5-dinitroacetophenone, the mixture immediately turns black and a mildly exothermic reaction takes place. After a few minutes at room temperature black crystals begin to appear, their formation being complete within 1 hr, yielding a compound (mp 178–180° from dioxane–water) hereafter referred to as compound Y (Table I).



Ia, $R_1 = R_2 = H$; $R_3 = NO_2$
b, $R_1 = COCH_3$; $R_2 = H$; $R_3 = NO_2$
c, $R_1 = CO_2Et$; $R_2 = H$; $R_3 = CN$

TABLE I
COMPOUND Y

Nmr (CF_3CO_2D)				Uv (MeOH)		Uv (66% H_2SO_4)	
δ	H	Multiplicity	*J*	λ	ε	λ	ε
0.8	6	Triplet	7.0 Hz				
3.4	4	Quartet	7.0 Hz				
2.5	3	Singlet		260	48,000	255	21,000
7.4[a]	1	Broad singlet		350	5,800	295	14,000
8.4[a]	1	Broad singlet		415	24,000	360	2,700
8.6[a]	1	Doublet	2.0 Hz	470	25,000	430	80
8.9[a]	1	Doublet	2.0 Hz	620	~0	550	~0

[a] The chemical shifts of these four protons are extremely solvent dependent, being well separated in trichloroacetic acid and mineral acids but having totally different positions in other solvents. For example, in chloroform or methylene chloride the two downfield protons accidentally overlap (2 H, δ 8.36), the two upfield protons now appearing at δ 7.5 and 7.1; while in dimethyl sulfoxide both the two downfield protons as well as the two upfield protons are accidentally overlapping at δ 8.7 and 7.3, respectively.

Elemental analysis established the empirical formula as $C_{15}H_{17}N_3O_4$ and a mass spectrum of the compound confirms it to have a molecular weight of 303. This corresponds to the combination of 1 equiv each of diethylamine, acetone, and 3,5-dinitroacetophenone, together with the loss of 1 molar equiv of hydrogen and water. The ir of Y shows the presence of acidic hydrogens or C=N multiple bonds. The uv of Y shows it not to be of the dinitropropenyl class, as such

(1) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).
(2) E. Bunchel, A. R. Norris, and K. E. Russel, *Quart. Rev., Chem. Soc.*, 123 (1963).
(3) R. Foster and C. A. Fyfe, *Tetrahedron*, **22**, 1831 (1962).
(4) H. Schran and M. J. Strauss, *J. Org. Chem.*, **36**, 856 (1971).
(5) M. J. Strauss, T. C. Jensen, H. Schran, and D. O'Conner, *J. Org. Chem.*, **35**, 383 (1970).

compounds have an absorption peak at 510 nm (ϵ 30,000–50,000).

Discussion

Reduction of Y with tin in hydrochloric acid resulted in a compound having a similar nmr except for the presence of amine hydrogens (4 H) at δ 3.8 and a shift of the aromatic peaks to δ 6.1, 6.5, 6.7, and 7.0. Treatment of this compound with acetic anhydride gave a diacetyl derivative with two methyl peaks at δ 1.8 and 2.0. These results are consistent with the presence of *two* nitro groups in Y.

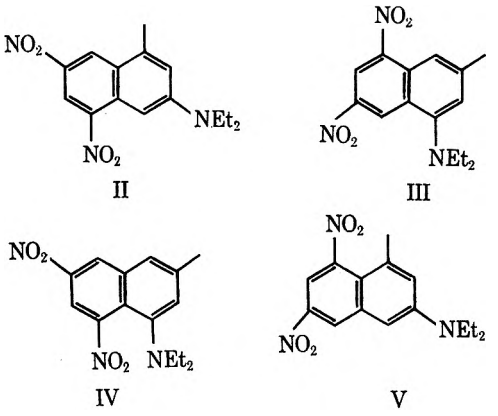
The intensely red colored Y is insoluble in water, but dissolves in concentrated mineral acids to give clear yellow solutions which yield unchanged Y upon dilution with water. Estimations of basicity of the compound in aqueous sulfuric acid solutions show it to have approximately the basicity of 3,5-dinitroaniline (pK_a = 0.23) but to be much more basic than 2,4-dinitroaniline. This finding suggests the presence of an amine nitrogen substituent on an aromatic ring bearing two meta nitro groups, or a direct through-conjugation with the nitro groups but across a much larger aromatic system. Such long-range conjugative effects have been observed previously, for example in the basicity of aminoquinolines.[6]

Subtracting the elements due to the methyl, diethylamino, and nitro moieties from the empirical formula $C_{15}H_{17}N_3O_4$, one is left with a skeletal formula of $C_{10}H_4$ which corresponds to a parent hydrocarbon, $C_{10}H_8$. All four of the protons not on side chains appear in the aromatic region of the nmr spectrum and show a meta coupling between the two downfield peaks. The only possible $C_{10}H_4$ aromatic skeletons consistent with these facts are naphthalenic and azulene structures containing meta-positioned hydrogens.[7]

The results of a deuterium exchange experiment allow the exclusion of the azulene structures. The compound Y exchanges *one* of its four ring protons (that at δ 8.4) for deuterium in trifluoroacetic acid-*O-d* with a half-life of *ca.* 30 min. This result is consistent with the naphthalenic structures, since naphthalene is electrophilically attacked at the α position an order of magnitude faster than at the β position.[8] Azulenes, on the other hand, exchange in the 1 and 3 positions in both acidic and basic media.[9] Neither of the protons in the 1 or 3 positions could exchange faster than the other owing to resonance influences of substituents on the azulene seven-membered ring, since in acidic exchange, the plus charge of the carbonium ion intermediate is delocalized equally onto all of the carbon atoms of the seven-membered ring. A two-proton exchange is thus obligatory and we are left only with naphthalenic backbone structures to consider.

The nmr aromatic region can always be divided into two meta-coupled downfield peaks and two meta-coupled upfield peaks. From known dependences of aromatic chemical shifts on ring substitution, the former set of protons can be assigned to the nitrated ring of a naphthalene structure, and the latter set of protons to the ring derived from acetone.

There are thus four remaining positional isomers of the remaining naphthalene possibilities, which are given below.



Models show one feature which distinguishes between structures III–V and structure II. In II the hydrogens of the methyl group are in intimate contact with the peri hydrogen on the nitrated ring. Space-filling models indicate that this hydrogen ought to actually restrict the rotational motion of the methyl group. This close spatial proximity combined with the lack of through-bond coupling between the two sets of protons is what is required for the transfer of spin relaxation energy from one set of nuclei to the other, *i.e.*, a nuclear Overhauser effect.[10]

In fact, saturation of the methyl protons in either the field or frequency sweep modes produced a marked reduction in the intensity of the δ 8.6 hydrogen. From known chemical shift dependences the hydrogen between the two nitro groups ought to be furthest downfield. Therefore the hydrogen in the α position of the nitrated ring ought to be the next upfield peak (that at δ 8.6). Reduction of the intensity of this peak with respect to the other aromatic peaks was observed as high as 50%. Overhauser effects of this magnitude can be unambiguously interpreted, and this fact, along with the other evidence presented above, clearly establishes the compound Y as having structure II.[11]

Structure II can be formed through a reasonable mechanism *via* an intermediate such as VI, which is known to be formed in the interaction of 3,5-dinitro-substituted aromatics with bases.[12] However, in this case, instead of another Michael attack on the benzene ring by the acetone enamine to form bicyclic structures like I, one obtains reactions with the active car-

(6) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," 2nd ed, Interscience, New York, N. Y., 1967, p 258.

(7) The pronounced stability of Y under a variety of vigorous reaction conditions renders an 8:4 system such as C unlikely.

C

(8) L. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold, New York, N. Y., 1961, p 879.

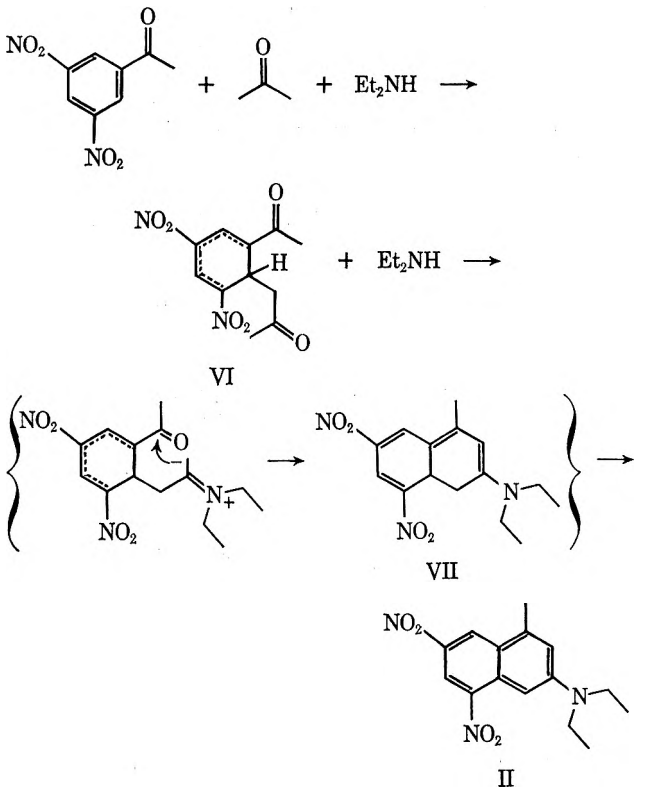
(9) B. C. Challis and F. A. Long, *J. Amer. Chem. Soc.*, **87**, 1196 (1965).

(10) R. A. Bell and J. K. Saunders, *Can. J. Chem.*, **46**, 3421 (1968).

(11) Attempts to use acetone-d_6 to distinguish among the naphthalene structures proved to be futile, as there was complete exchange of deuterium between acetone-d_6 and the acetophenone methyl prior to product formation.

(12) M. J. Foreman, R. Foster, and M. J. Strauss, *J. Chem. Soc. B*, 147 (1970).

bonyl position to yield a dihydronaphthalene structure like VII, which then aromatizes to form the product II.



Attempts were made to make derivatives of Y by treating 3,5-dinitroacetophenone and diethylamine with 1-phenylacetone, acetylacetone, or 2-butanone. However, all of these compounds failed to give isolable products. This inability to obtain products from ketones other than acetone can be rationalized in terms of structure II in that there must be too great a steric interaction in the 1,2,3- or 3,4,5-trisubstituted naphthalenes to allow the reaction to go to completion in the presence of competing side ractions.

In order to investigate the generality of the reaction it was decided to change the nature of the aromatic starting material.

When an acetone solution of 3,5-dinitrobenzaldehyde (prepared from the acid chloride and lithium tributoxyaluminum hydride[13]) was treated with diethylamine, an instant black color formed and a mildly exothermic reaction proceeded. Within a few minutes black crystals were growing from the solution, which after recrystallization gave a material with mp 183.5–185.6° in a yield of 47%.

Similarly to the original compound Y, this material was soluble in polar media to give dark red solutions. It was not soluble in water but gave a pale yellow solution in mineral acids. The molecular weight was 289, which corresponds to one CH_2 group less than Y. Analysis of the compound gave an empirical formula of $C_{11}H_{15}N_3O_4$.

The uv and visible spectra show a series of peaks with an envelope identical in essential features with that of Y, indicating that the substance belongs to the same structural class as II.

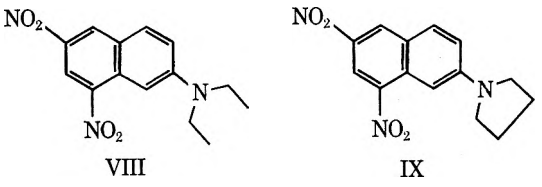
(13) R. N. Zaxapkah, A. H. Mosach, and R. B. Raepurecko, *Zh. Org. Khim.*, **2**, 2197 (1966).

The nmr of the material shows the presence of two ethyl moieties and *five* aromatic peaks. By analogy with structure assignment II for compound Y, there is now an expected definite AB pattern in the aromatic region of this new material (J = 9 cps).

Synthesis of the material from acetone-d_6 produced a spectrum whose AB pattern was partially collapsed (incompletely owing to prereaction exchange between acetone-d_6 and diethylamine), which reveals that one of the protons in the AB pattern is derived from acetone and the other is a proton originating from the benzaldehyde.

As in the original compound II, this material exchanges only one proton in trifluoroacetic acid-*O*-*d*, which is the third upfield proton.

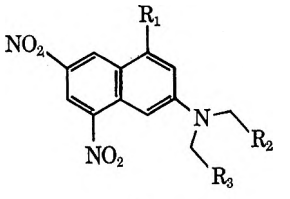
All of these findings are consistent with structure VIII for this second compound.



As a check on the generality of the reaction, pyrrolidine was allowed to react with acetone and 3,5-dinitrobenzaldehyde. The reaction mixture proved to be very exothermic and had to be kept on ice for the first few minutes to prevent boiling to dryness. This reactivity might be expected, as pyrrolidine has a much higher propensity to form enamines than diethylamine. After crystallization from dioxane a 30% yield of black crystals was obtained, mp 229–231°.

The compound had a molecular weight of 287 and an nmr analogous to that of VIII. It was found that exchange of one of the aromatic protons in the pyrrolidine derivative was very fast (half-life in minutes) in trifluoroacetic acid-*O*-*d*, which is again consistent with pyrrolidine's greater stability in the iminium form than diethylamine. Also, this material exchanges the single aromtic proton in 75% D_2SO_4–D_2O with a half-life of *ca.* 1 hr. These findings are all consistent with structure IX.[14]

It thus appears that compounds of the general structure X can be made through the reaction of the



appropriate alkylphenone, acetone, and secondary amine.[15]

(14) As can be seen from the structures II and III–V, the acetophenone methyl is an inherent part of the aromatic structure in compounds III–V, but is only a side chain in compound II. Thus observation of products VIII and IX with 3,5-dinitrobenzaldehyde is an independent proof of structure II *vs.* III–V.

(15) No attempts have been made to improve yields. However, as it is probable that 1 equiv of starting material is used in accepting the 1 equiv of hydrogen liberated in forming product, an oxidizing agent in the reaction mixture might considerably increase yields.

Experimental Section

3,5-Dinitroacetophenone.—Though this compound has been reported in the literature[16,17] from the reaction of 3,5 dinitrobenzoyl chloride and diethylmagnesium malonate, in our hands ethyl 3,5-dinitrobenzoate was always the major product. Included here, therefore, is a procedure which was patterned after that for the synthesis of *m*-nitroacetophenone.[18]

A three-necked 2-l. flask fitted with an addition funnel, a condenser with a nitrogen inlet, and a mechanical stirrer was charged with 16 g of magnesium turnings, and purged with nitrogen. To the flask was added 14.7 ml of absolute ethanol and 3 ml of carbon tetrachloride. After the reaction had subsided, 440 ml of anhydrous ether was added and then a solution of 103 ml (0.55 mol) of diethyl malonate, 59 ml (1.0 mol) of absolute ethanol, and 73 ml of ether was dropped in at a rate sufficient to cause rapid boiling. After refluxing for 4 hr, the ether was distilled off and approximately 200 ml of benzene was added. A continuous process of benzene addition and benzene–ethanol azeotropic distillation was carried out until the temperature was ~75° to remove the last of the ethanol. At this point, 1 l. of benzene was added to the pot, and the addition funnel was charged with a solution of 500 ml of benzene containing 135 g (0.59 mol) of 3,5-dinitrobenzoyl chloride. The stirring motor was placed on high speed, and the acid chloride solution was allowed to run into the pot as rapidly as possible. If the addition funnel has a sufficiently large bore stopcock, the addition takes approximately 15 sec, which gives the solution about 5 sec of high-speed stirring before the entire contents suddenly jell into a solid mass.

This material was then isolated and decarboxylated as in ref 18. The solid material so obtained was recrystallized from methanol, ethanol, or a 1:1 mixture of methanol–carbon tetrachloride to give 88 g (71%) of material, mp 81–83° (lit.[16] mp 80–81°).

In the following procedures high-quality 3,5-dinitroacetophenone must be used (commercial material fails to react without extensive purification) and the diethylamine and acetone must be dry. No attempts to maximize yields were undertaken other than to observe that excess amine decreases yields as does allowing the amine and acetone to mix before reaction with the aromatic compound.

1-Methyl-3-diethylamino-5,7-dinitronaphthalene (II).—To a solution of 1.5 g (0.007 mol) of 3,5-dinitroacetophenone in 4 ml of acetone was added 0.5 g (0.007 mol) of diethylamine. The solution was swirled and set aside. After 1 hr the solution was cooled in the refrigerator and then filtered. The black crystals thus obtained were washed (quickly) with acetone and then with ether. Crystallization from a 5:1 mixture of dioxane–water gave 0.7 g (32%) of II, mp 178–180°. *Anal.* Calcd for $C_{13}H_{17}N_3O_4$: C, 59.40; H, 5.61; N, 13.85. Found: C, 59.42; H, 5.71; N, 14.16. Further data can be found in the text.

1,3-Dinitro-7-pyrrolidinonaphthalene (IX).—To an ice-cold solution of 0.75 g (0.0037 mol) of 3,5-dinitrobenzaldehyde in 3 ml of acetone was added 0.27 g (0.0037 mol) of pyrrolidine. The solution was swirled and kept on ice for 15 min, whereupon it was filtered and the collected solid was rapidly washed with acetone. The crystals were taken up in 45 ml of boiling dioxane, which was then filtered. Cooling of the solution yielded 0.27 g of crystals. Addition of water to the hot, concentrated dioxane mother liquor until turbidity yielded on cooling another 0.07 g of material to give a total of 0.33 g (30%) of IX, mp 229–231°. *Anal.* Calcd for $C_{14}H_{13}N_3O_4$: C, 58.10; H, 5.19; N, 14.52. Found: C, 58.10; H, 5.22; N, 14.73. Nmr in CF_3CO_2D showed a broad singlet (4 H) at δ 2.6 and similarly (4 H) at δ 4.2, an AB pattern (2 H, J = 9 Hz) centered at δ 8.4, and two singlets (1 H, 1 H) at δ 9.5.

1,3-Dinitro-7-diethylaminonaphthalene (VIII).—To a solution of 1.0 g (0.0048 mol) of 3,5-dinitrobenzaldehyde in 3 ml of acetone was added 0.37 g (0.0048 mol) of diethylamine. The solution was swirled and set aside at room temperature for 30 min and worked up as above. The yield was 0.58 g (47%) of material, mp 183.5–185.6°. Nmr (CF_3CO_2D) showed a triplet (6 H, J = 7.5 Hz) at δ 1.48, a quartet (4 H, J = 7.5 Hz) at δ 4.08, an AB pattern (2 H, J = 9.0 Hz) at δ 8.6, a singlet (1 H) at δ 9.4, and a singlet (2 H) at δ 9.6.

Reduction of II.—To a steam-heated solution of 2 g of III in 150 ml of 38% HCl and 20 ml of concentrated sulfuric acid was added portionwise 4 g of tin with shaking over a period of 1 hr. The solution was basified with 50% aqueous NaOH and extracted with ether. After drying and treatment with activated charcoal, yellow crystals were obtained (0.5 g), mp 96–97°. Nmr ($CDCl_3$) showed a triplet (6 H, J = 8 Hz) at δ 1.18, a singlet (3 H) at δ 2.68, a quartet (4 H, J = 8 Hz) at δ 3.4, a singlet (4 H) at δ 3.88, a doublet (2 H, J = 0.5 Hz) at δ 6.08, a singlet (1 H, broad) at δ 6.5, a singlet (1 H) at δ 6.7, and a singlet (1 H) at δ 7.0.

To 0.35 g of this material in 20 ml of ether was added 1 ml of acetic anhydride. After 0.5 hr of stirring the solution was poured into water, neutralized with sodium bicarbonate, and extracted with methylene chloride. The methylene chloride solution was stirred with ammonium hydroxide for 0.5 hr and extracted with water and the solvent was evaporated. The residue was crystallized from methanol to give 0.25 g of material, mp 139.5–141.0°. Nmr ($CDCl_3$) showed a triplet (3 H, J = 8 Hz) at δ 1.18, a singlet (3 H) at 1.88, two singlets (3 H, 3 H) at δ 2.3 and 2.08, a quartet (4 H, J = 8 Hz) at δ 3.2, and singlets (1 H, 1 H, 2 H, 1 H, 2 H) at δ 6.48, 6.78, 7.10, 8.08, and 8.28, respectively.

Acknowledgments.—The author would like to acknowledge Professor C. G. Swain for financial support and the National Science Foundation for a predoctoral fellowship, 1970–1971. He would also like to express his indebtedness to Professor D. Kemp for many helpful discussions during the course of this work.

Registry No.—II, 40792-03-8; VIII, 40792-04-9; IX, 40792-05-0; II reduction product, 40792-22-1; II reduction product, diacetyl derivative, 40792-23-2; 3,5-dinitroacetophenone, 14401-75-3; diethyl malonate, 105-53-3; 3,5-dinitrobenzoyl chloride, 99-33-2; acetone, 67-64-1; diethylamine, 109-89-7; 3,5-dinitrobenzaldehyde, 14193-18-1; pyrrolidine, 123-75-1.

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New Synthetic Reactions. Dimethylsulfonium 2-Oxotetrahydrofuryl-3-ylide as an Annelating Reagent[1]

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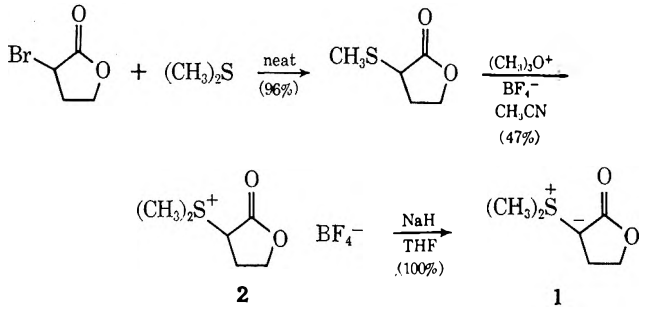
Alkylation of α-methylthio-γ-butyrolactone available from 2-bromo-γ-butyrolactone with trimethyloxonium fluoroborate followed by deprotonation with sodium hydride generates dimethylsulfonium 2-oxotetrahydrofuryl-3-ylide. This new annelating reagent combines with acrolein, methyl vinyl ketone, acrylonitrile, dimethyl fumarate, diethyl maleate, and benzalacetophenone to give the corresponding cyclopropanes in 25–90% yields in a highly stereoselective reaction. Nonenolizable 1,2-dicarbonyl compounds also condense to give a glycidic lactone but in low yield. Some transformations of the acrolein adduct are described. Treatment of 2-methylthio-γ-butyrolactone with lithium diisopropylamide generated the corresponding enolate as demonstrated by deuteration and methylation. Attempts to condense this enolate with cyclohexanone failed.

The utility of sulfur ylides (π sulfuranes) in synthesis has encouraged the development of new types of ylides and the exploration of their synthetic potential.[3] As a result many alkyl-substituted ylides[4] and ylides stabilized by carboxylate,[5] carboalkoxy,[6] acyl,[7] and cyano[8] groups have been developed. The existence of many geminal-substituted cyclopropanes in which the alkyl groups are differentially functionalized encouraged us to examine the synthesis and reactions of dimethylsulfonium 2-oxotetrahydrofuryl-3-ylide.[9] Use of such a reagent would introduce geminal cyclopropyl groups at the oxidation level of an alcohol and an ester.

The ylide was obtainable as a somewhat stable solid which would decompose over a period of weeks in the freezer by deprotonation of *S,S*-dimethyl-*S*-(2-oxotetrahydro-3-furyl)sulfonium fluoroborate (2) with sodium hydride (Scheme I). The latter was readily

SCHEME I
GENERATION OF YLIDE 1



2 1

available by the methylation of α-methylthio-γ-butyrolactone, the disproportionation product of dimethyl sulfide and 2-bromo-γ-butyrolactone. The ylide 1 showed an exceedingly low carbonyl stretch at 1647 cm^{-1}, indicating extensive delocalization of negative charge. The approximately 30-cm^{-1} shift from that of dimethylsulfonium carboethoxymethylide (3)

$$(CH_3)_2S{=}CHCO_2C_2H_5$$
3

(1620 cm^{-1})[6] is what is expected for placement of the carbonyl in a five-membered ring. The nmr spectrum exhibits two approximate triplets (J = 8 Hz) at δ 4.30 and 2.75 for the ring protons and a singlet at δ 2.68 for the *S*-methyl groups. The shift of only 0.1 ppm from the salt to the ylide for the *S*-methyl groups compares to a 0.4-ppm shift for the same change in the case of ylide 3. The fixed cisoid configuration in the lactone ylide 1 accounts for this difference.[10] Attempts to generate the ylide with hydroxylic base led only to decomposition.

Condensation of the preformed ylide with Michael acceptors gave mixed results (see Scheme II). Good Michael systems such as acrylonitrile, benzalacetophenone, diethyl maleate, dimethyl fumarate, acrolein, and methyl vinyl ketone generated the desired cyclopropanes in yields from 12 to 90%. Synthetically, it is sometimes advantageous to prepare the ylide in the presence of the Michael acceptor. Thus, in the case of chalcone, the adduct 9 was obtained in 92% yield (based on sulfonium salt 2) by generating the ylide *in situ* with sodium hydride, whereas with the preformed ylide, the yield of adduct was only 12% (based on ylide 1). In order to explore this question further, the reaction of acrylonitrile was examined in more detail (see Table I). The lower yields obtainable in DMF or HMPA may be attributable to the instability of the ylide in these solvents. The stability factor also poses a problem in acetonitrile and tetrahydrofuran, as evidenced by the increase in yield as a function of increasing the ratio of trapping agent to ylide. Synthetically, the best overall yields of cyclopropanes are obtained by use of *in situ* ylide generation and of an approximately 2:1 ratio of Michael acceptor to ylide. Acetonitrile appears to be the best solvent for reactions with preformed ylide.

The structures of the adducts are clearly supported by spectroscopic data. The ir spectra had a lactone

(1) Part 12 of our series on new synthetic reactions.

(2) Camille and Henry Dreyfus Teacher–Scholar Grant Recipient.

(3) For some reviews see C. Agami, *Bull. Soc. Chim. Fr.*, 1021 (1965); J. C. Bloch, *Ann. Chim. (Paris)*, **10**, 419 (1965); A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966; P. A. Lowe, *Chem. Ind. (London)*, 1070 (1970). For the fundamental papers in synthetic applications see E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965), and V. Franzen, H. J. Schmidt, and C. Mertz, *Chem. Ber.*, **94**, 2942 (1961).

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(8) D. Jeckel and J. Gosselck, *Tetrahedron Lett.*, 2101 (1972); B. M. Trost and L. S. Melvin, Jr., unpublished work.

(9) *Cf.* H. Nozaki, D. Tunemoto, S. Matubara, and K. Kondo, *Tetrahedron*, **23**, 545 (1967).

(10) J. Casanova and D. A. Rutolo, *Chem. Commun.*, 1224 (1967).

SCHEME II

MICHAEL REACTIONS OF YLIDE 1

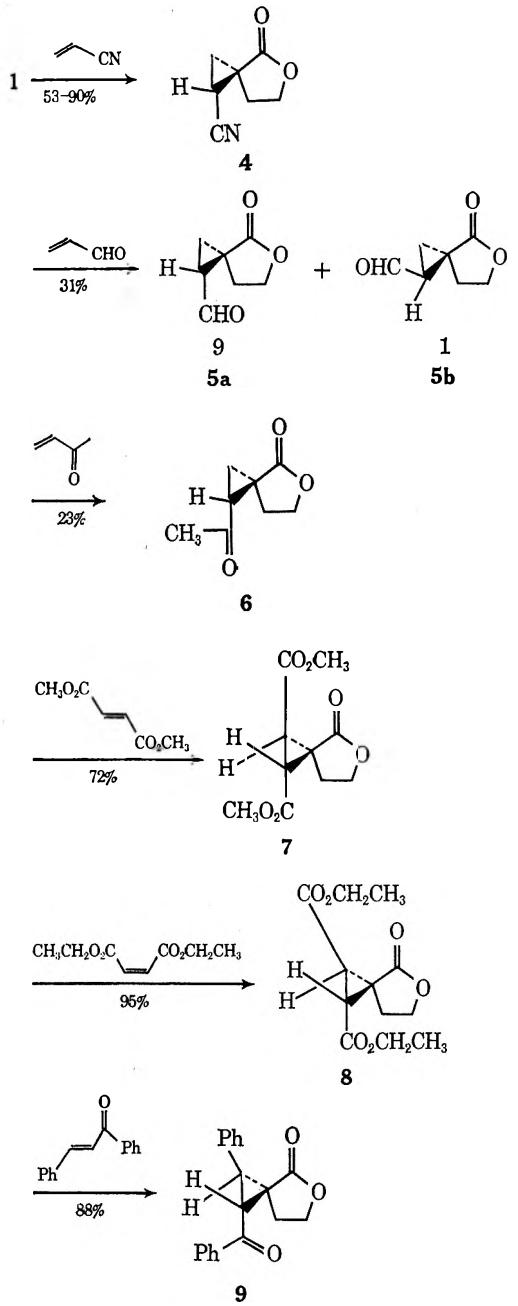


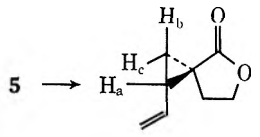
TABLE I

YIELD DATA FOR ADDUCT 4[a]

Mode of ylide generation	Ratio ylide: acrylonitrile	Solvent	Time, hr	Yield, %
1, Preformed	1:1	CH_3CN	8	58[b]
2, *In situ*	1:1	THF	8	64[c]
3, *In situ*	1:2	THF	8	75[c]
4, *In situ*	1:4	THF	8	84[c]
5, *In situ*	1:1	DMF	8	17[c]
6, *In situ*	1:1	HMPA	6	21[c]

[a] All runs carried out at room temperature and all yields are of isolated product. [b] Yield based on starting ylide 1. [c] Yield based on starting salt 2.

carbonyl at 1770–1775 cm^{-1}. The rest of the spectral data is summarized in the Experimental Section. In each case examined, condensation generated one major cyclopropane isomer whose stereochemistry is assigned in structures **4**–**9**. The stereochemistry of adduct **5** was most thoroughly investigated. Its nmr spectrum showed two aldehyde proton absorptions at δ 9.62 and 9.28 in the ratio of 9:1. Since the carboxaldehydo group of **5b** lies directly in the shielding cone of the lactone carbonyl, the higher field absorption was assigned to this isomer. Treatment of the aldehyde with triphenylphosphonium methylene produced the olefin **10** as an essentially single isomer after chromato-



graphic separation. The cyclopropane protons appear at δ 2.02 (ddd, J = 8.9, 6.4, 5.1 Hz), 1.50 (dd, J = 8.9, 4.5 Hz), and 0.90 (dd, J = 6.4, 4.5 Hz) assignable to H_a, H_b, and H_c, respectively, on the basis of relative chemical shifts, cyclopropyl cis coupling being larger than trans coupling,[11] and pseudocontact shift data.[12] Upon addition of 20 mol % of Eu(fod)$_3$ the absorptions at δ 1.50 and 0.90 shift to δ 2.40 and 1.40, respectively, indicating that H_b is cis to the lactone carbonyl and H_c trans. The shift of H_a from δ 2.02 to 3.10, combined with the coupling constants, demands that it is cis to the lactone carbonyl.

For adduct **6**, the protons of the cyclopropyl methylene group appear as a simple doublet at δ 1.4 (J = 7.2 Hz) in the nmr spectrum, indicating that each is in the same magnetic environment, *i.e.*, cis to a carbonyl group as in structure **6**. Such accidental equivalence would not be explicable on the basis of the alternative isomer. Similarly, adducts **7** and **8** show nonequivalent ester groups in their nmr spectra (see Experimental Section) demanding the trans isomers. The stereochemistry of the remaining adducts are assigned on the basis of analogy to the above and earlier work.[5–8]

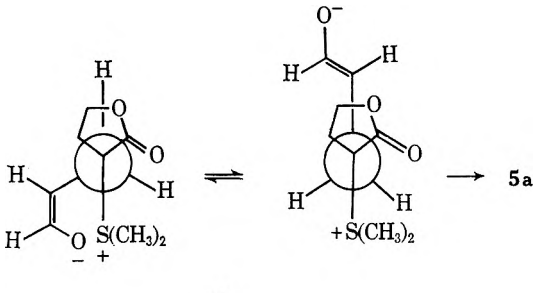
Stabilized ylides add reversibly to α,β-unsaturated systems to generate intermediate enolates, thus the loss of olefin stereochemistry in the product.[5–9] The stereochemical preferences seen normally reflect the thermodynamic stability of these intermediates. In considering the conformers for the precursors of **5a** and **5b** (**11a** and **11b**, respectively), clearly steric and unfavorable dipole–dipole interactions are minimized in **11a** compared to **11b**, thus accounting for the stereoselectivity observed.

Less reactive Michael acceptors such as ethyl 3-methyl-2-butenoate, carvone, and methyl sorbate failed to react. Carbonyl condensations with cyclohexanone and benzaldehyde were also unsuccessful. 1,2-Dicarbonyl systems gave mixed results. Biacetyl and methyl pyruvate failed to condense, presumably because of enolization under the reaction conditions. Benzil, which cannot enolize, did condense, although in low yields, to produce adduct **12**.[13] Its infrared spectrum showed carbonyl absorptions at 1785 and 1670 cm^{-1}. The nmr spectrum showed only the typical pattern for the CH_2CH_2 unit of the lactone ring in

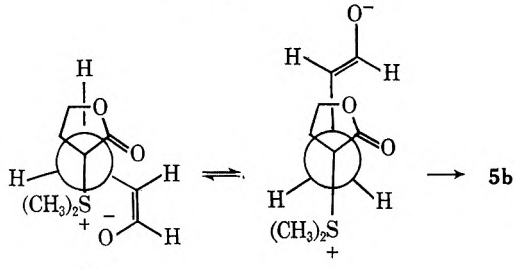
(11) J. D. Graham and M. T. Rogers, *J. Amer. Chem. Soc.*, **84**, 2249 (1962); A. Bothner-by, *Advan. Magn. Resonance*, **1**, 195 (1965).

(12) P. E. Manni, G. A. Howie, B. Katz, and J. M. Cassady, *J. Org. Chem.*, **37**, 2769 (1972).

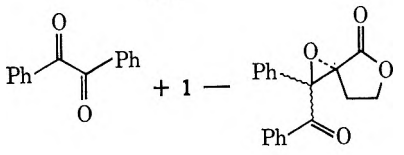
(13) For a glycidic lactone see J. D. White, J. B. Bremner, M. J. Dimsdale, and R. L. Garcea, *J. Amer. Chem. Soc.*, **93**, 7398 (1971).



11a



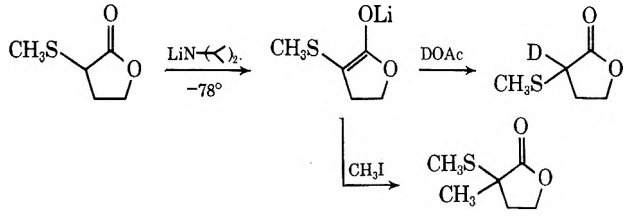
11b



12

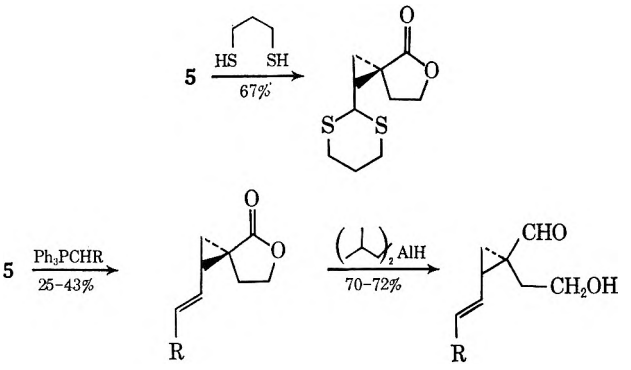
addition to aromatic absorptions but did suggest that the adduct was essentially stereohomogeneous.

To overcome this unreactivity, a brief investigation centered on the generation and properties of the anion of α-methylthio-γ-butyrolactone.[14] Dropwise addition of the sulfide to a −78° solution of lithium diisopropylamide in THF followed by quenching with DOAc generated the corresponding 2-deuterio-2-methylthio-γ-butyrolactone, which was 65% d_1, by nmr and mass spectral analysis.[15] Addition of 1 equiv of methyl



iodide to the anion generated the methylated compound in 37% yield. However, attempts to condense cyclohexanone with the lactone enolate led to essentially quantitative recovery of starting materials. Its failure to undergo ketone condensation may be due to enolization.

In ancillary experiments, some transformations of the cyclopropane adducts were investigated. Adduct **5** formed a dithiane derivative quite smoothly, although attempts to desulfurize this adduct failed. The aldehyde underwent Wittig condensation with triphenylphosphonium methylide and crotylide to give olefin lactones **10** and **13**. Reduction of the lactone to



10, R = H
13, R = CH=CHCH$_3$

the lactol proceeded smoothly with diisobutylaluminum hydride. It is interesting to note that the product exists solely in the hydroxyaldehyde form as evidenced by the carbonyl stretching frequency at 1700 cm^{-1} in the infrared spectrum and the aldehyde proton at δ 8.80–9.06. Such products would be valuable intermediates to the dictyopterenes.[16]

Experimental Section

General.—Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Infrared spectra were determined on a Beckman IR-8 spectrophotometer, and ultraviolet spectra were recorded on Cary Model 11 and Model 15 spectrophotometers. Nmr spectra were determined on Varian Associates Model A-60A, HA-100, or XL100 spectrometers fitted with a variable-temperature probe. Chemical shifts are given in parts per million relative to TMS as an internal standard. Abbreviations for multiplicity are s, singlet; d, doublet; app t, apparent triplet; t, triplet; and m, multiplet. Mass spectra were taken on a MS-902 mass spectrometer at an ionizing current of 40 mA and ionizing voltage of 70 V. Analyses were performed by Spang Microanalytical Laboratory. Vpc analyses were performed on an Aerograph Model 90P instrument. Tlc separations were achieved on Merck (Darmstadt) silica gel PF-254. All reactions were carried out under an atmosphere of nitrogen.

Preparation of α-Methylthio-γ-butyrolactone.—A mixture of 58.2 g (0.35 mol) of α-bromo-γ-butyrolactone and 85 g (100 ml, 1.37 mol) of dimethyl sulfide was refluxed for 20 hr under a nitrogen atmosphere. After the mixture was allowed to cool, filtration removed the precipitated trimethylsulfonium bromide, which was washed thoroughly with ether. The ether washes were combined with the original filtrate and the solvent was removed *in vacuo*, leaving a pale yellow oil. Distillation under reduced pressure yielded 44.6 g (96%) of α-methylthio-γ-butyrolactone: bp 82–86° (0.5 mm); ir (CCl_4) 1779 cm^{-1}; nmr (CCl_4) δ 2.25 (3 H, s), 2.3–3.0 (2 H, m), 3.24 (1 H, dd, J = 8.2, 5.4 Hz), and 4.34 (app t, J = 7.2 Hz); mass spectrum m/e (rel intensity) 132 (59), 122 (5), 120 (4), 86 (100), 73 (45), and 55 (44).

Anal. Calcd for $C_5H_8O_2S$: 132.02450. Found: 132.02457.

Preparation of Dimethyl(2-oxotetrahydro-3-furyl)sulfonium Fluoroborate (3).—α-Methylthio-γ-butyrolactone (30 g, 0.23 mol) was dissolved in 750 ml of dry (freshly distilled from calcium hydride) acetonitrile under nitrogen. Trimethyloxonium fluoroborate (33.6 g, 0.23 mol) was added in one portion. After the mixture was stirred for 1.5 hr at room temperature, the solvent was removed *in vacuo* and the residual oil was swirled with ether. After the ether washes were decanted, the residue was dissolved

(14) For other studies on enolates derived from lactones see A. E. Greene, J. C. Müller, and G. Ourisson, *Tetrahedron Lett.*, 2489 (1972); P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972); G. H. Posner and G. L. Loomis, *ibid.*, 892 (1972).

(15) The less than 100% deuterium incorporation is presumably due to isotope dilution because of the presence of protonic diisopropylamine. A similar effect has been found in quenching enolates of esters generated in similar fashion. See M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 2318 (1971).

(16) For a leading reference see J. A. Pettus and R. E. Moore, *J. Amer. Chem. Soc.*, **93**, 3087 (1971).

in 20 ml of dry acetonitrile and absolute ethanol was added to precipitate the sulfonium salt. The resultant solid was recrystallized twice from ethanol–acetonitrile to give 25 g (47%) of sulfonium salt: mp 81.5–82.5°; ir (Nujol) 1748 cm^{-1}; nmr (CO_3CN) δ 2.1–3.0 (2 H, m), 3.02 (3 H, s), 3.05 (3 H, s), and 4.3–4.8 (3 H, m).

Anal. Calcd for $C_6H_{11}O_2SBF_4$: C, 30.75; H, 4.74; S 13.66; F, 32.47. Found: C, 30.86; H, 4.55; S, 13.82; F, 32.60.

Preparation of Dimethylsulfonium 2-Oxotetrahydrofuryl-3-ylide (1).—Sodium hydride (257 mg, 6.00 mmol, of a 56% dispersion in mineral oil) was washed free of mineral oil with pentane under a nitrogen atmosphere. Subsequently, 50 ml of dry tetrahydrofuran (distilled from sodium benzophenone ketyl) and then 1.50 g (6.4 mmol) of salt 2 were added. Stirring continued at room temperature until evolution of hydrogen ceased. The solution was decanted from a solid residue. The latter was washed with chloroform and the chloroform layer was combined with the tetrahydrofuran solution. Evaporation *in vacuo* produced a gum which was induced to crystallize by dissolving in ethanol and adding ether. In this way, 880 mg (quantitative yield) of ylide 1 was obtained. For infrared and nmr spectral data see results and discussion section. 1 had uv ((CH_3CN) λ_{max} 263 nm (ϵ 107); mass spectrum *m/e* (rel intensity) 146 (7), 132 (59), 100 (42), 98 (62), 86 (100), and 73 (45).

Anal. Calcd for $C_6H_{10}O_2S$: 146.04015. Found: 146.04055.

Reaction of π Sulfurane 1 with Acrylonitrile. Method A (*in Situ* Generation).—A suspension of 192 mg (4.5 mmol of a 56% mineral oil dispersion) of sodium hydride, 1.10 g (4.70 mmol) of dimethyl(2-oxotetrahydro-3-furyl)sulfonium fluoroborate, and 984 mg (18.6 mmol) of acrylonitrile in 25 ml of dry tetrahydrofuran was prepared under nitrogen. This mixture was stirred for 8 hr at room temperature. The mixture was then poured into water and extracted with ethyl acetate. After drying over anhydrous magnesium sulfate and removal of solvent *in vacuo*, a nearly colorless oil remained. Chromatographic separation by tlc eluting with chloroform and washing the product off the silica gel with ether gave 544 mg (84%) of cyclopropane 4: ir ($CHCl_3$) 2250 and 1768 cm^{-1}; nmr ($CDCl_3$) δ 4.48 (2 H, app t, J = 7 Hz), 2.50 (2 H, app t, J = 7 Hz), 2.05 (1 H, dd, J = 8.5, 6.7 Hz), 1.52 (1 H, dd, J = 8.5, 4.5 Hz), and 1.46 (1 H, dd, J = 6.7, 4.5 Hz); mass spectrum *m/e* (rel intensity) 137 (7), 136 (4), 119 (5), 109 (12), 84 (39), 56 (100), and 55 (59).

Anal. Calcd for $C_7H_7O_2N$: 137.04767. Found: 137.04762.

Method B (Preformed).—Dimethylsulfonium 2-oxotetrahydrofuryl-3-ylide (385 mg, 2.64 mmol) was dissolved in 25 ml of dry acetonitrile (distilled from calcium hydride) under nitrogen. Acrylonitrile (152 mg, 2.87 mmol) was added in one portion and the solution was stirred for 8 hr at room temperature. The reaction mixture was evaporated *in vacuo* and the crude product was chromatographed on silica gel utilizing chloroform as the eluting solvent. In this way 209 mg (58%) of cyclopropane 4 identical with the material previously characterized was obtained.

Reaction of π Sulfurane 1 with Benzalacetophenone.—As described above for the *in situ* method (method A), 1.00 g (4.3 mmol) of salt 2, 182 mg (4.3 mmol) of a 56% mineral oil dispersion of sodium hydride, and 930 mg (4.4 mmol) of benzalacetophenone in 30 ml of THF was converted to 1.1 g (88%) of crystalline product 9, mp 106.5–107°, after tlc purification utilizing benzene as the eluting solvent: uv (C_2H_5OH) λ_{max} 248 nm (ϵ 10,700); nmr ($CDCl_3$) δ 8.1 (2 H, m), 7.72 (3 H, m), 7.4 (5 H, pseudosinglet), 4.47 (2 H, app t, J = 7.7 Hz), 3.98 (1 H, d, J = 7 Hz), 3.47 (1 H, d, J = 7 Hz), 2.52 (2 H, app t, J = 7.7 Hz); mass spectrum *m/e* (rel intensity) 292 (3), 187 (5), 128 (3), 105 (100), and 77 (17).

Anal. Calcd for $C_{18}H_{16}O_3$: C, 78.05; H, 5.86; mol wt, 292.10994. Found: C, 77.70; H, 5.59; mol wt, 292.10886.

Reaction of π Sulfurane 1 with Diethyl Maleate.—As described above for method B, 137 mg (0.94 mmol) of π sulfurane 1 and 147 mg (0.85 mmol) of freshly distilled diethyl maleate in 25 ml of dry acetonitrile generated 209 mg (95%) of 8 after tlc isolation utilizing chloroform as the eluting solvent: ir ($CHCl_3$) 1775 and 1725 cm^{-1}; nmr ($CDCl_3$) δ 4.43 (2 H, app t, J = 7.2 Hz), 4.18 (2 H, q, J = 7 Hz), 4.15 (2 H, q, J = 7 Hz), 2.2–3.0 (4 H, m), 1.28 (3 H, t, J = 7 Hz), and 1.23 (3 H, t, J = 7 Hz); mass spectrum *m/e* (rel intensity) 256 (1), 186 (32), 185 (26), 177 (12), 144 (100), 132 (32), 129 (51), 115 (22), 86 (48), 84 (70), 73 (24), and 55 (30).

Anal. Calcd for $C_{12}H_{16}O_6$: 256.09468. Found: 256.09503.

Reaction of π Sulfurane 1 with Dimethyl Fumarate.—By method B, 350 mg (2.4 mmol) of π sulfurane 1 and 376 mg (2.6 mmol) in 20 ml of acetonitrile gave 390 mg (72%) of crystalline 7, mp 93.5–94.0°, after tlc purification utilizing chloroform as the eluting solvent: ir ($CHCl_3$) 1772 and 1726 cm^{-1}; nmr ($CDCl_3$) δ 4.48 (2 H, app t, J = 7.2 Hz), 4.12 (3 H, s), 4.05 (3 H, s), 2.90 (1 H, d, J = 6.8 Hz), 2.68 (1 H, d, J = 6.8 Hz), and 2.50 (2 H, app t, J = 7.2 Hz).

Reaction of π Sulfurane 1 with Methyl Vinyl Ketone.—Preformed dimethylsulfonium 2-oxotetrahydrofuryl-3-ylide (251 mg, 1.72 mmol) was dissolved in 25 ml of dimethylformamide (freshly distilled from calcium hydride) at room temperature. In one portion, 131 mg (1.87 mmol) of methyl vinyl ketone was added and the solution was stirred for 7 hr at room temperature. It was then poured into 150 ml of water and extracted with 3 × 25 ml of ethyl acetate. The ethyl acetate extracts were washed with 3 × 50 ml of water to remove dimethylformamide. After the extracts were dried over anhydrous potassium carbonate and the solvent was removed *in vacuo*, the product was purified by tlc utilizing chloroform as the eluting solvent to give 62 mg (23%) of 6 as an oil: ir ($CHCl_3$) 1769 and 1705 cm^{-1}; nmr ($CDCl_3$) δ 4.28 (2 H, app t, J = 7.5 Hz), 2.47 (1 H, t, J = 7.2 Hz), 2.25 (3 H, 3), 2.22 (2 H, app t, J = 7.5 Hz), and 1.40 (2 H, d, J = 7.2 Hz); mass spectrum *m/e* (rel intensity) 154 (6), 139 (23), 136 (100), 112 (58), 111 (82), 108 (75), 95 (58), 83 (43), 67 (93), and 53 (53).

Anal. Calcd for $C_8H_{10}O_3$: 154.06299. Found: 154.06359.

Reaction of π Sulfurane 1 with Acrolein.—By method A, 10 g (42.7 mmol) of salt 2, 1.83 g (38.0 mmol) of 56% mineral oil dispersion of sodium hydride, and 2.39 g (42.7 mmol) of acrolein in 250 ml of dry tetrahydrofuran produced 1.65 g (31%) of cyclopropane 5 as a colorless oil after silica gel chromatography utilizing chloroform as the eluting solvent: ir ($CHCl_3$) 2730, 1772, and 1705 cm^{-1}; nmr ($CDCl_3$) δ 9.62 (1 H, d, J = 3 Hz), 4.45 (2 H, app t, J = 7.1 Hz), 2.55 (1 H, ddd, J = 10.1, 7.1, 3.0 Hz), 2.43 (2 H, app t, J = 7.1 Hz), and 1.40–2.1 (2 H, m); mass spectrum *m/e* (rel intensity) 140 (8), 122 (14), 109 (74), 91 (54), 86 (58), 79 (100), 77 (68), and 71 (98). In the nmr spectrum a doublet also appeared at δ 9.28 (J = 6 Hz). Utilizing the relative intensity of this signal to the one at δ 9.62 gave an isomer ratio of 1:9.

Anal. Calcd for $C_7H_8O_3$: 140.08372. Found: 140.08314.

Preparation of Glycidic Lactone 12.—To a solution of 267 mg (1.83 mmol) of ylide 1 in 20 ml of dry acetonitrile was added 418 mg (2.0 mmol) of benzil at room temperature. The mixture was stirred for 2.5 hr at room temperature and 2 hr at 84°. After cooling and evaporation of solvent, the crude material was chromatographed on silica gel utilizing chloroform as the eluting solvent. In this way, 76 mg (14% yield) of glycidic lactone, mp 139–140°, was obtained in addition to a recovery of 260 mg (62%) of benzil: ir ($CHCl_3$) 1785, 1670, 1590, and 1580 cm^{-1}; nmr ($CDCl_3$) δ 8.0 (2 H, m), 7.1–7.8 (8 H, m), 4.46 (2 H, app t, J = 7.0 Hz), and 2.47 (2 H, app t, J = 7.0 Hz); uv (C_2H_5OH) 254 nm (ϵ 8200); mass spectrum *m/e* (rel intensity) 294 (5), 249 (7), 165 (3), 116 (5), 105 (100), and 77 (29).

Anal. Calcd for $C_{18}H_{14}O_4$: 294.08920. Found: 294.08741.

Reaction of Cyclopropyl Aldehyde 5 with Wittig Reagents. Reaction with Triphenylphosphonium Methylide.—To a slurry of 4.32 g (12.0 mmol) of methyltriphenylphosphonium bromide in 95 ml of dry tetrahydrofuran (distilled from sodium benzophenone ketyl) was added 9.16 ml (12.0 mmol) of a 1.31 *M* hexane solution of *n*-butyllithium and the mixture was stirred for 20 min. A solution of 1.65 g (11.7 mmol) of aldehyde 5 in 5 ml of dry tetrahydrofuran was added in one portion at room temperature and the mixture was subsequently heated to 60° for 15 hr. The slurry was cooled and filtered to remove the precipitated triphenylphosphine oxide. The solvent was removed *in vacuo* and the crude material was chromatographed on 1 kg of silica gel G utilizing chloroform as eluting solvent. In this way 698 mg (44%) of the methylene compound 10 was obtained as a colorless oil: ir ($CHCl_3$) 1765, 1640, 985, and 909 cm^{-1}; nmr ($CDCl_3$) δ 5.27 (3 H, m), 4.33 (2 H, app t, J = 6.9 Hz), 2.23 (2 H, app t, J = 6.9 Hz), 2.02 (1 H, ddd, J = 8.9, 5.1, 4.5 Hz), 1.50 (1 H, dd, J = 8.9, 4.5 Hz), and 0.9 (1 H, dd, J = 6.4, 4.5 Hz); mass spectrum *m/e* (rel intensity) 138 (17), 137 (4), 123 (30), 110 (17), 93 (41), 91 (37), 79 (100), 77 (55), 66 (24), and 53 (27).

Anal. Calcd for $C_9H_{10}O_2$: 138.06807. Found: 138.06733.

Reaction with Triphenylphosphonium Crotylide.—As described above, 470 mg (1.20 mmol) of crotyltriphenylphosphonium bromide, 888 μl (1.16 mmol) of a 1.31 *M* hexane solution of *n*-

butyllithium, and 162 mg (1.15 mmol) of aldehyde **5** were converted into 50 mg (25%) of diene **13** after isolation by tlc utilizing chloroform as eluting solvent: ir ($CHCl_3$) 1773 cm^{-1}; nmr ($CDCl_3$) δ 4.6–6.5 (4 H, m), 4.22 (2 H, app t, J = 7.6 Hz), 2.27 (2 H, app t, J = 7.6 Hz), 1.9–2.3 (1 H, m), 1.79 and 1.73 (3 H, overlapping d, J = 6.0 Hz), 1.4 (1 H, m), and 0.95 (1 H, m); mass spectrum m/e (rel intensity) 178 (70), 163 (10), 150 (51), 133 (30), 119 (38), 105 (67), 93 (31), 91 (100), 81 (76), 80 (100), 79 (71), and 77 (53).

Anal. Calcd for $C_{11}H_{14}O_2$: 178.09937. Found: 178.09942.

Preparation of Dithiane Derivative of Aldehyde 5.—To a solution of 150 mg (1.07 mmol) of aldehyde **5** in 10 ml of chloroform at 0° was added 129 mg (1.2 mmol) of 1,3-propanedithiol and 150 μl of distilled boron trifluoride etherate. After stirring for 45 min, the reaction mixture was diluted with 50 ml of ether and washed with 2 × 50 ml of saturated aqueous sodium bicarbonate solution. After drying over anhydrous potassium carbonate, the solvent was removed *in vacuo*. Purification by tlc utilizing chloroform as eluting solvent yielded 170 mg (69%) of product as a colorless oil: ir ($CHCl_3$) 1755 cm^{-1}; nmr ($CDCl_3$) δ 4.47 (2 H, app t, J = 7.9 Hz), 3.47 (1 H, d, J = 10.1 Hz), 2.8 (4 H, m), 2.41 (1 H, dd, J = 6.7, 4.8 Hz), 2.0 (2 H, m), 1.55 (2 H, m); mass spectrum m/e (rel intensity) 230 (12), 132 (100), 123 (6), 106 (6), 99 (7), 97 (6), 73 (6), and 58 (6).

Anal. Calcd for $C_{10}H_{14}O_2S_2$: 232.05917. Found: 232.06102.

Preparation of 1-(2′-Hydroxyethyl)-2-vinylcyclopropanecarboxaldehyde. To a solution of olefin lactone **10** (26 mg, 0.19 mmol) in 3 ml of dry toluene cooled to −78° was added 140 μl (0.20 mmol) of a 1.42 M diisobutylaluminum hydride solution in toluene. The reaction was stirred for 5 min and then quenched by addition of 1 ml of absolute ethanol. The reaction mixture was poured into 5 ml of saturated aqueous ammonium chloride solution and 0.5 ml of glacial acetic acid was added. The product was extracted with ethyl acetate and the combined organic layers were washed with 20 ml of saturated aqueous sodium bicarbonate solution. After drying over anhydrous potassium carbonate and evaporation *in vacuo*, isolation of product was accomplished by tlc utilizing a 95:5 (v/v) chloroform–ether mixture to give 18 mg (70%) of product: ir (CCl_4) 3390, 2720, 1700, and 1635 cm^{-1}; nmr ($CDCl_3$) δ 8.84 (1 H, s), 4.9–5.9 (3 H, m), 3.70 (2 H, app t, J = 6.5 Hz), 2.64 (1 H, brs), 1.93 (1 H, ddd, J = 8.9, 7.0, 3.3 Hz), 1.51 (1 H, dd, J = 8.9, 5.0 Hz), and 1.13 (1 H, dd, J = 7.0, 5.0 Hz); mass spectrum m/e (rel intensity) 140 (8), 122 (14), 121 (12), 109 (74), 91 (54), 86 (58), 81 (60), 79 (100), 77 (68), 71 (98), 70 (44), 58 (88), and 53 (51).

Anal. Calcd for $C_8H_{12}O_2$: 140.08372. Found: 140.08314.

Preparation of 1-(2′-Hydroxyethyl)-2-(1″,3″-pentadienyl)-cyclopropanecarboxaldehyde.—As described above, 50 mg (0.28 mmol) of diene lacetone **13** upon treatment with 196 μl (0.28 mmol) of a 1.42 M toluene solution of diisobutylaluminum hydride in 3 ml of toluene yielded 36 mg (72%) of aldehyde product after tlc purification utilizing a 95:5 (v/v) mixture of chloroform–ether as the eluting solvent: ir ($CHCl_3$) 3571, 2717, 1700, and 1620 cm^{-1}; nmr ($CDCl_3$) δ 9.08, 8.89, and 8.81 (total 1 H, all s), 4.8–6.5 (4 H, m), 3.72 (2 H, app t, J = 6.3 Hz), 1.4–2.6 (6 H, m with superimposed singlet at 2.62 and doublets at 1.78 and 1.73), and 1.1 (1 H, m).

Metalation of α-Methylthio-γ-butyrolactone.—To a solution of 1.01 g (10 mmol) of diisopropylamine in 11 ml of dry tetrahydrofuran at −78° was added 8.86 ml (11.6 mmol) of n-butyllithium (1.3 M in hexane) over a 2-min period. After the solution was stirred for an additional 15 min, 1.32 g (10.0 mmol) of α-methylthio-γ-butyrolactone was added dropwise. Upon completion of the addition, stirring was continued for 15 min. Freshly distilled methyl iodide (1.42 g, 10.0 mmol) was added all at once. Reaction proceeded for another 15 min at −78° and slowly warmed to room temperature. Addition of 20 ml of water quenched the reaction and the products were extracted with ether. After drying over anhydrous potassium carbonate, the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography utilizing chloroform as eluting solvent to give 541 mg (37%) of α-methyl-α-methylthio-γ-butyrolactone: ir (CCl_4) 1760 cm^{-1}; nmr ($CDCl_3$) δ 4.28 (2 H, m), 2.2–2.7 (2 H, m), 2.14 (3 H, s), and 1.53 (3 H, s); mass spectrum m/e (rel intensity) 146 (35), 100 (100), 98 (14), 87 (20), 69 (18), and 55 (47).

Anal. Calcd for $C_6H_{10}O_2S$: 146.04015. Found: 146.04047.

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Registry No.—**1**, 40587-47-1; **2**, 40733-71-9; **4**, 40587-48-2; **5a**, 40587-49-3; **5b**, 40587-43-7; **6**, 40587-44-8; **7**, 40587-45-9; **8**, 40587-46-0; **9**, 40587-50-6; **10**, 40587-51-7; **12**, 40587-52-8; **13**, 40587-53-9; α-methylthio-γ-butyrolactone, 40587-54-0; α-bromo-γ-butyrolactone, 5061-21-2; dimethyl sulfide, 75-18-3; acrylonitrile, 107-13-1; benzalacetophenone, 94-41-7; diethyl maleate, 141-05-9; dimethyl fumarate, 624-49-7; methyl vinyl ketone, 78-94-4; acrolein, 107-02-8; benzil, 134-81-6; triphenylphosphonium crotylide, 40587-56-2; 1,3-propanedithiol, 109-80-8; dithiane derivative of **5**, 40587-57-3; 1-(2′-hydroxyethyl)-2-vinylcyclopropanecarboxaldehyde, 40587-58-4; 1-(2′-hydroxyethyl)-2-(1″,3″-pentadienyl)cyclopropanecarboxaldehyde, 40587-59-5; α-methyl-α-methylthio-γ-butyrolactone, 40587-60-8.

Synthesis of Tricyclo[4.4.1.1^{2,5}]dodec-3-en-11-one

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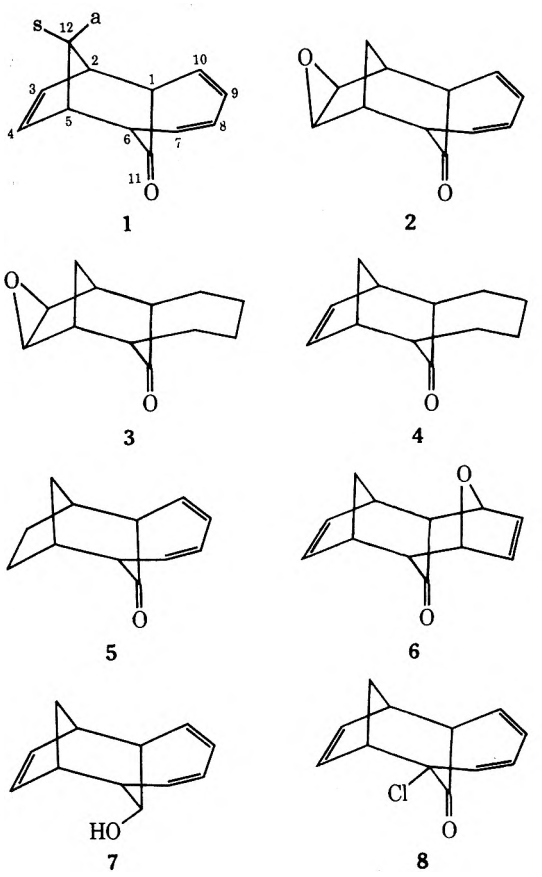
To convert tricyclo[4.4.1.1^{2,5}]dodeca-3,7,9-trien-11-one (1) into tricyclo[4.4.1.1^{2,5}]dodec-3-en-11-one (4), it was necessary to protect the isolated double bond while hydrogenation of the conjugated diene was accomplished. Both *m*-chloroperbenzoic acid and chlorine react selectively with the isolated double bond to give, respectively, an exo epoxide and a trans dichloride which are retained during hydrogenation of the remaining diene unit, and from which the isolated double bond can be regenerated. Regeneration from the epoxide fails with reagents which attack the sterically hindered carbon atom of the heterocycle (sodium iodide, zinc and acetic acid, and triphenylphosphine) but is facile with reagents which attack the unhindered epoxide oxygen atom (chromous ion and zinc–copper couple). Regeneration of the olefin from the dichloride is readily effected with zinc in refluxing ethanol. In the present example, which is one of the first employing protecting groups for this purpose, it is clear that the conversion *via* the dichloride is the superior route. Some of the spectral properties (nmr, ir, and uv) of the various compounds prepared are presented and discussed and some of the nmr parameters of the tricyclo[4.4.1.1^{2,5}]dodecyl and norbornyl ring systems compared.

A frequently encountered and often vexing synthetic problem is that of protecting one functional group while reactions are carried out on another. Although the literature abounds with examples of protecting groups, there are relatively few examples of ones which protect specifically one double bond in the presence of another.[1] We would like to report the use of two groups that we have used to protect an isolated double bond while a reaction is carried out on a distant diene unit.

As part of our general interest in the use of rigid polycyclic molecules as stereochemical models, it became necessary to synthesize tricyclo[4.4.1.1^{2,5}]dodec-3-en-11-one (4), the most promising precursor of which is the well-known tricyclo[4.4.1.1^{2,5}]dodeca-3,7,9-trien-11-one (1),[2] formed from tropone and cyclopentadiene. We initially considered reducing the activity of the isolated double bond of 1 (it is hydrogenated more readily than is the diene unit[2a]) by chlorine substitution in the cyclopentadiene starting material, but the direction taken by this cycloaddition can be greatly altered by substitution in the addends;[3] in particular neither 1,2,3,4-tetrachlorocyclopentadiene[3a] nor hexachlorocyclopentadiene add to tropone to give derivatives of **1**. It was thus necessary to protect the isolated double bond of **1**.

Reaction of **1** with 1 equiv of *m*-chloroperbenzoic acid[4,5] afforded *exo*-3,4-epoxytricyclo[4.4.1.1^{2,5}]dodeca-7,9-dien-11-one (**2**) in addition to some unidentified minor products. The ir spectrum of **2** shows all the bands typical of epoxides.[6] The uv spectrum is almost identical with that reported for **5**[2a] and eliminates other conceivable, symmetrical but unconjugated structures such as **6**; in fact the uv parameters of this diene chromophore have proven to be very diagnostic in **1**, in a variety of its derivatives (Table I) and in related compounds.[7] The nmr spectrum, discussed more fully below, establishes that **2** has a plane of symmetry, the same ring structure as **1**, and the exo stereochemistry as shown.



(1) *Cf.* J. F. W. McOmie, *Advan. Org. Chem.*, **3**, 191 (1963).

(2) (a) R. C. Cookson, B. V. Drake, J. Hudec, and A. Morrison, *Chem. Commun.*, 15 (1966); (b) S. Itô, Y. Fujise, T. Okuda, and Y. Inoue, *Bull. Chem. Soc. Jap.*, **39**, 1351 (1966); S. Itô, K. Sakan, and Y. Fujise, *Tetrahedron Lett.*, 2873 (1970).

(3) (a) Y. Kitahara, I. Murata, M. Funamizu, and T. Asano, *Bull. Chem. Soc. Jap.*, **37**, 1399 (1964); (b) S. Itô, K. Sakan and Y. Fujise, *Tetrahedron Lett.*, 775 (1969).

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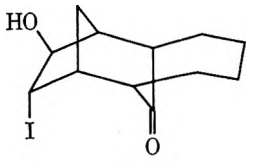
Catalytic hydrogenation of **2** gave the saturated epoxide *exo*-3,4-epoxytricyclo[4.4.1.$1^{2,5}$]dodecan-11-one (**3**). Retention of the epoxide ring was shown spectroscopically, in particular by the ir bands,[6] and by the nmr singlet at τ 6.73.

Several procedures are commonly used for the regeneration of olefins from epoxides.[8] Treatment of **3** with sodium iodide, zinc and acetic acid,[9] or triphenylphosphine and hydroquinone[10] according to the published procedures gave only recovered **3**. Both of these reagents attack epoxide rings stereospecifically from the back side of one of the carbon atoms to give, respectively, a trans iodohydrin,[9] *e.g.*, **9**, and a trans betaine,[11] *e.g.*, **10**, which then undergo elimination to give an olefin, *e.g.*, **4**. We feel that the deoxygenation fails with both reagents at the ring opening rather than at the elimination step. Cornforth, Cornforth, and Mathew treated epoxides with iodide ion and isolated iodohydrins which were subsequently converted to olefins with zinc;[9] however, **3** failed to react with iodide ion with or without zinc present. Although direct elimination of triphenylphosphine oxide from **10** is untenable because it requires rotation about the C-3–C-4 bond to eclipse the phosphorus and oxygen atoms and leads to the highly strained trans olefin **11**, it is



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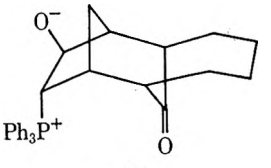

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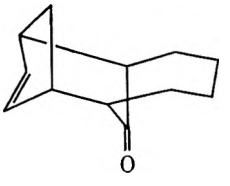

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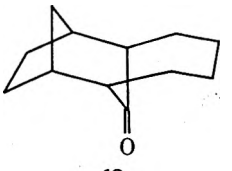
expected[12] that **10** will equilibrate *via* ylide intermediates with either of its cis epimers, from which elimination should be facile. We thus conclude that neither **9** nor **10** is formed because the required attack by the bulky nucleophiles from the endo side of **3** is too sterically hindered.

An alternative mode of epoxide ring opening, attack by the phosphorus at the oxygen atom (unhindered in **3**), is the predominant, if not the exclusive, route in the closely related desulfurization of episulfides.[13] It is not the commonly found pathway for deoxygenation, however, and one considered unlikely on theoretical grounds.[14] Our results are the first experimental evidence that epoxide deoxygenation by a trivalent phosphorus compound will not occur by this route should the preferred attack at carbon be impossible.

In contrast to the two reagents discussed above, both zinc–copper couple[15] and chromous ion[15,16] deoxygenate **3** readily, giving **4** as the sole product (overall yield from **1**, *ca.* 30%). The structure of **4** followed from its method of preparation, its conversion upon mild catalytic hydrogenation into the known ketone **12**,[2a] and its

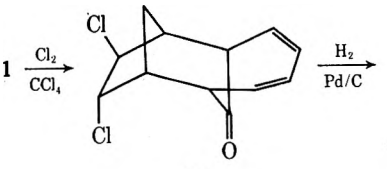


12

nmr spectrum. These two reagents effect the desired deoxygenation because they attack the unhindered epoxide oxygen atom of **3**[15,16] rather than one of the hindered carbon atoms.

We have also found that the isolated double bond in **1** can be protected as its dichloride. Trienone **1** reacted with chlorine to give *trans*-3,4-dichlorotricyclo[4.4.1.$1^{2,5}$]dodeca-7,9-dien-11-one (**13**) as the predominant product. As with **2**, structural assignment of **13** rested on spectral evidence which clearly showed the presence of the diene chromophore and the trans relationship of the chlorine atoms.

Catalytic hydrogenation of **13** gave *trans*-3,4-dichlorotricyclo[4.4.1.$1^{2,5}$]dodecan-11-one (**14**), whose



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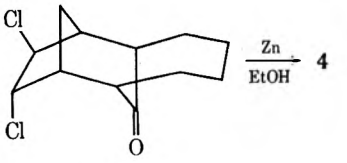

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structure was assigned by nmr. Treatment of **14** with zinc in refluxing ethanol effected removal of the blocking group to give the desired ketone **4** (overall yield from **1**, *ca.* 35%).

It is apparent from this work that both epoxidation and chlorination occur selectively at the isolated double bond of **1** and therefore usefully protect that function in the presence of the conjugated diene unit. Chlorination appears to be more selective than epoxidation in agreement with its larger value of ρ[4d] and the unlikelihood of competing reactions at the carbonyl group. The generality of these two protecting procedures awaits additional work, however, since it is not yet certain that diene units react more slowly with electrophiles than do nonconjugated olefins, or if the present example of selectivity has some other origin, for example, an exceptionally reactive C-3–C-4 bond or diene

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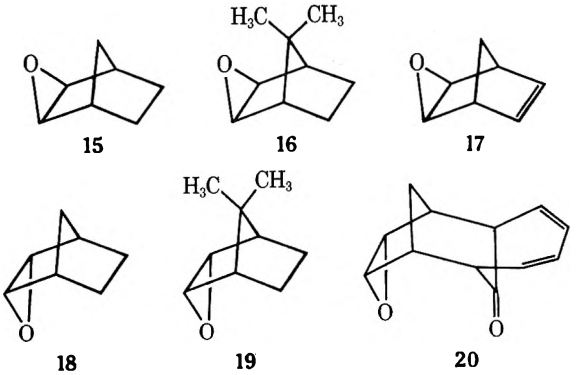
deactivation by the nearby carbonyl group.[4] Extensions of our studies on the spectroscopic and chemical properties of **4** and some of its derivatives are currently in progress.

Nmr Spectra.—The nmr spectra of the tricyclo[4.4.1.1^{2,5}]dodecane derivatives prepared in this study have proven to be very useful for stereochemical and structural assignments and to demonstrate that this ring system has much in common with the norbornyl one.

The epoxide ring protons in **2** appear as a sharp singlet at almost the same postion as the sharp signals exhibited by the exo epoxides **15**,[17] **16**,[18] and **17**;[19] the endo epoxides **18**[18] and **19**[18] give signals which are broader and at somewhat lower field than those of their exo counterparts.[20] Although it is tempting to assign the exo stereochemistry to **2** on the basis of this chemical shift data alone, we do not feel that such an argument is justified at this time because the anisotropic effects of the bonds in **1** on protons at C-3 and C-4 are as yet unknown, because the chemical shift differences between the known exo–endo pairs of epoxides is relatively small, and because only one isomer of **2** is yet available. The stereochemistry of **2** can be assigned from the observed coupling, however.

Each of the four exo epoxides **2**, **15**, **16**, and **17** displays a very sharp signal for the epoxide ring protons, owing to a very small coupling to the adjacent bridgehead protons, whereas the endo epoxides **18** and **19** show a broader, more strongly coupled signal. This coupling pattern is typical of *exo*- and *endo*-norbornyl[21] and more pertinently of *exo*- and *endo*-tricyclo[3.2.1.0^{2,4}]octyl[22] derivatives. The implied similarly between the norbornyl and the tricyclo[4.4.1.1^{2,5}]dodecyl systems is supported by molecular models which indicate little geometric change upon removal of the C-1–C-6 bond, the dihedral angles between H-2 and H-3 being about 75° in **2** (small coupling) and about 5° in the as yet unknown **20** (larger coupling).[23] The corresponding angles measured for **15** and **18** are 60 and 20°, respectively, so that the coupling difference between *exo*- and *endo*-norbornyl derivatives should be enhanced in the tricyclo[4.4.1.1^{2,5}]dodecyl system.



Corroborative evidence for both the similarity between the two ring systems and the assigned stereochemistry of **2** comes from a consideration of the bridge protons. It has finally been established that the H-7a proton of norbornene absorbs at higher field than H-7s.[24] The assignment of the bridge proton signals in **1** and its derivatives rests on the examination of molecular models, which indicate that the complex, highest field signal is due to H-12s (dihedral angle about 40°) whereas the simple, lower field doublet is due to H-12a (dihedral angle about 80°). Although the relative positions of the syn and anti protons in **1** and norbornene are opposite, epoxidation to **2** and **15** is accompanied by identical behavior: an upfield shift of about 0.3 ppm of the anti proton, the syn proton being relatively ununaffected. This parallel behavior of the bridge protons strengthens the arguments for an exo stereochemistry in **2** and emphasizes the geometric similarity between the norbornyl and tricyclo[4.4.1.1^{2,5}]dodecyl ring systems.

The two dichlorides **13** and **14** have also provided interesting nmr spectra. The assignment of the two protons H-3 and H-4 was based on the relative chemical shifts of *trans*-2,3-dichloronorbornene,[21] in which H-2$_{exo}$ is at lower field, and on the larger coupling to the adjacent bridgehead expected for the exo proton. A more rigorous analysis is required to more firmly assign the chemical shifts and coupling constants in these rather complex molecules.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The nmr spectra were obtained on a Varian A-60A spectrometer in deuteriochloroform solution. Peak positions are given in units of τ relative to internal tetramethylsilane at τ 10.00; in all cases the relative peak areas are consistent with assigned structure. Infrared spectra were recorded as Nujol mulls or as neat liquids on a Unicam SP200 spectrometer; the peak positions are recorded in wavenumbers. Ultraviolet spectra (Table I) were recorded on a Unicam SP800 recording uv spectrophotometer using ethanol as the solvent. Gas–liquid chromatograms (glc) were obtained on a Varian-Aerograph A90P3 instrument using a single column of Carbowax 20M (25%) packed on acid-washed Chromosorb W. Combustion microanalyses were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn. 37921.

TABLE I

ULTRAVIOLET SPECTRA OF SOME TRICYCLO[4.4.1.1^{2,5}]DODEC-7,9-DIENES

Compd	Band positions (ϵ)[a]	Ref
1[b]	267 (4935) 258 (4600) 249 (3375) 240 (2730) 216 (3510)	
1[c]	267 (7870) 257 (7680)	2a
1[b,d]	266 (4630) 257 (4520) 248 (3370) 238 (2840)	2b
5[c]	269 (4620) 258 (4720)	2a
2[b]	266 (6075) 256 (6000) 248 (4100) 239 (2800sh) 222 (3500)	
13[b]	270 (4080) 260 (4280) 252 (3075) 243 (2100sh) 223 (2440)	
7[d]	273 (3173) 262 (5568) 252 (5720) 243 (4552sh)	2b
8	270 (4040) 261 (4100) 252 (3070)	3b

[a] λ_{max} in nm obtained in ethanol unless otherwise stated. [b] In addition a broad weak peak (ϵ *ca.* 500) was noted at *ca.* 300 nm. [c] Solvent not specified. [d] Methanol as solvent.

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(20) *endo*-Norbornadiene oxide, the endo analog of **17**, has been reported but no nmr data were given. See J. T. Lumb and G. H. Whitham, *J. Chem. Soc.*, 1189 (1964), and ref 19.

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(23) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

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Reaction of Tropone and Hexachlorocyclopentadiene.—An nmr tube containing a mixture of 230 mg of freshly distilled tropone, 600 μl of acetone, and 655 mg of freshly distilled hexachlorocyclopentadiene was heated at 60°. After 21 hr the tube contents had turned black with the deposition of black particles but the nmr had not changed. The reaction was discontinued.

Tricyclo[4.4.1.1^{2,5}]dodeca-3,7,9-trien-11-one (1).—This ketone, mp 69.5–70.0° (lit.[2] mp 70–71.5°), was prepared in 65% yield by a modification of the published route. It was found advantageous to monitor the reaction by nmr, to distill off the volatile components at the completion of the reaction, and to purify the product by column chromatography followed by recrystallization. The nmr spectrum showed peaks at τ 3.8–4.6 (m, H-3, H-4, H-7–H-10), 6.7–6.9 (m, H-1, H-6), 6.9–7.05 (m, H-2, H-5), 7.68 (d, H-12a, J = 11 Hz), 8.50 (dt, H-12s, J = 11, 5.5 Hz).

***exo*-3,4-Epoxytricyclo[4.4.1.1^{2,5}]dodeca-7,9-dien-11-one** (2).—A mixture of 1.00 g of 1 and 1.24 g of 85% *m*-chloroperbenzoic acid in 15 ml of chloroform was stirred at room temperature until a positive test with starch iodide paper was no longer obtained (*ca.* 2–5 hr). Additional chloroform was added to dissolve a white precipitate and the organic solution was washed with 10% aqueous sodium carbonate solution and water and then dried over magnesium sulfate. The drying agent was filtered off and the solvent was evaporated to give a yellow oil which deposited sticky crystals on standing. The product was chromatographed on a column of alumina eluting unreacted 1 (benzene), mixtures of 1 and 2 (benzene), and mixtures of 2 and an as yet unidentified third component (benzene and ether).

Unreacted 1 could be separated from 2 by virtue of its greater solubility in ether to leave an analytically pure sample of 2, mp 141.5–142°, sublimation of which [115° (0.2 mm)] depressed the melting point somewhat (139.5–142°). The ir spectrum showed characteristic peaks at 3050, 1710, 1280, 1260, 900, and 840 cm^{-1}. The nmr spectrum showed peaks at τ 3.80–4.65 (m, H-7–H-10), 6.65 (s, H-3, H-4), 6.68–6.95 (m, H-1, H-6), 7.26–7.48 (m, H-2, H-5), 7.95 (d, H-12a, J = 13 Hz), 8.63 (dt, H-12s, J = 13, 5.5 Hz).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.76; H, 6.40.

The yield of 2 was very difficult to determine because of the difficulty of separating it from the unidentified product.

***exo*-3,4-Epoxytricyclo[4.4.1.1^{2,5}]dodecan-11-one** (3).—The crude product from the epoxidation of 1.10 g of 1 (*vide supra*) was dissolved in 75 ml of 95% ethanol and exposed to hydrogen gas in the presence of 400 mg of 10% palladium on charcoal. After the hydrogen uptake ceased (400 ml) the catalyst was removed by filtration and the solvent was evaporated to give a yellow oil which was purified by chromatography on alumina. Benzene elution afforded 0.16 g of tricyclo[4.4.1.1^{2,5}]dodecan-11-one (12) from hydrogenation of unreacted 1,[25] followed closely by 0.39 g (32% from 1) of pure 3, sublimation of which [100° (1.0 mm)] gave an analytical sample, mp 88.5–89.5°. The ir spectrum showed characteristic peaks at 1690, 1265, 1250, 890, and 850 cm^{-1}. The nmr spectrum showed peaks at τ 6.73 (s, H-3, H-4), 7.10–7.50 (m, H-1, H-6), 7.50–7.70 (t, H-2, H-5, J = 4 Hz), 7.75–8.85 (m, H-7–H-12).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.08; H, 8.51.

An additional 0.64 g of a yellow oil, as yet unidentified, was obtained by further elution with methanol. The only volatile component of this oil had a shorter retention time (glc) than 3 and was present in smaller amounts (ratio *ca.* 1:2.5).

Treatment of 3 with Zinc–Copper Couple.—The method of Kupchan and Maruyama[15] was followed. Zinc–copper couple was prepared from 900 mg of zinc as usual[26] except that the ether wash and drying were omitted. A mixture of this couple, 3 ml of ethanol, and 102 mg of 3 was sealed in a thick-walled glass tube, which had been flushed out with nitrogen, and heated at 140° for 24 hr. The mixture was cooled to room temperature and filtered and the solvent was evaporated to give 93 mg (99%) of glc homogeneous, white, crystalline 4. Sublimation [110° (10 mm)] gave an analytical sample, mp 60.5–61.5°. The ir spectrum showed peaks at 3020 and 1710 cm^{-1}; the nmr spectrum showed peaks at τ 3.89 (s, H-3, H-4), 7.3–7.5 (m, H-1, H-2, H-5, H-6), 7.56 (d, H-12a, J = 12 Hz), and 7.9–8.7 (m, H-7–H-10, H-12s).

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.62; H, 9.18.

Longer reaction times caused further reduction to 18; milder conditions (reflux for 70 hr) gave only 2% reaction.

Treatment of 3 with Cr(II).—A solution of $Cr(ClO_4)_2$ was prepared according to the method of Kupchan and Maruyama.[15] To a thoroughly degassed (argon) solution of 40 mg of 3 in 12 ml of *N*,*N*-dimethylformamide was added 1.2 ml of the Cr(II) solution and 60 μl of ethylenediamine. This solution was stirred and heated at 90° for 5 hr under a slow stream of argon. The mixture was cooled to room temperature, poured into 20 ml of 2 *N* aqueous hydrochloric acid, and extracted three times with ether. The ether was washed with 10% aqueous sodium carbonate and dried over magnesium sulfate. The drying agent was filtered off and the solvent was evaporated to give a yellow oil. The product was purified by chromatography on alumina. Benzene eluted 25 mg (68%) of pure 4 identical with that prepared above.

Treatment of 3 with Triphenylphosphine.—The procedure of Wittig and Haag[10] was followed. A mixture of 100 mg of 3, 138 mg of triphenylphosphine, and 21 mg of hydroquinone was heated to 180° over a period of 1 hr and kept at that temperature for an additional 2.5 hr. The black reaction mixture was cooled to room temperature and chromatographed on a 10-g column of alumina. Benzene (25 ml) eluted triphenylphosphine (80 mg) and unreacted 3 (100 mg) cleanly separated from it. The nmr spectrum of the recovered 3 was identical with that of authentic material and showed no trace of the expected product 4.

Treatment of 3 with Sodium Iodide.—This experiment was based on the published procedure.[9] A mixture of 100 mg of 3, 164 mg of sodium iodide, 17 mg of sodium acetate, 0.3 ml of acetic acid, and 0.6 ml of propionic acid was heated at 100° for 18 hr. The mixture was diluted with ether, washed with 10% aqueous sodium bicarbonate solution, sodium bisulfite solution, and water, and dried over magnesium sulfate. The drying agent was filtered off and the solvent was evaporated to give a yellow solid. The nmr spectrum showed that it was unreacted 3.

Treatment of 3 with Sodium Iodide and Zinc.—The method used was that described by Cornforth, Cornforth, and Mathew.[9] An ice-cooled solution of 134 mg of sodium iodide and 45 mg of sodium acetate in 0.27 ml of acetic acid and 0.02 ml of water was prepared and 134 mg of zinc powder was added to it. To this magnetically stirred mixture was added 100 mg of 3, which caused the suspension to turn brown and then gray and very pasty. After standing at 0° for about 75 min the mixture was filtered and the residues were washed well with ether. The organic solution was washed with 10% aqueous sodium carbonate solution and water and dried over magnesium sulfate. The drying agent was filtered off and the solvent was evaporated to give 60 mg of a yellow solid shown to be unreacted 3 by comparison of its nmr spectrum with that of an authentic sample.

***trans*-3,4-Dichlorotricyclo[4.4.1.1^{2,5}]dodeca-7,9-dien-11-one** (13).—A solution of 1.64 g of chlorine in 25 ml of carbon tetrachloride was added to a solution of 4.05 g of trienone 1 in 115 ml of carbon tetrachloride at room temperature. After about 0.5 hr of stirring the initial green color had disappeared and an additional 1.64 g of chlorine in 25 ml of carbon tetrachloride was added. After a total reaction time of 1 hr the solvent was evaporated to give a viscous green oil which was decolorized by elution with ether through a short alumina column followed by treatment with charcoal in ethanol. Evaporation gave yellow crystals which were rechromatographed on alumina using ether as the eluent giving 4.7 g of crude white product, the nmr of which clearly showed 13 to be the predominant component. Recrystallization (ether) afforded 2.15 g (37%) of pure 13. Additional material was present in the mother liquors. Sublimation [125° (0.4 mm)] gave an analytical sample, mp 156–156.5°. The ir spectrum showed peaks at 1720, 800, and 700 cm^{-1}. The nmr spectrum showed peaks at τ 3.80–4.70 (m, H-7–H-10), 5.45–5.70 (m, H-4$_{exo}$, J = 4.2, 6.4 Hz), 6.00 (dd, H-3$_{endo}$, J = 4.2, 2.4 Hz), 6.27–6.85 (m, H-1, H-6), 7.15–7.55 (m, H-2, H-5, H-12a), 8.02 (ddt, H-12s, J = 13.7, 4.6, 1.0 Hz).

Anal. Calcd for $C_{12}H_{12}Cl_2O$: C, 59.28; H, 4.98; Cl, 29.16. Found: C, 59.23; H, 4.91; Cl, 29.08.

***trans*-3,4-Dichlorotricyclo[4.4.1.1^{2,5}]dodecan-11-one** (14).—A solution of 4.09 g of 13 in 300 ml of 95% ethanol was exposed to hydrogen gas in the presence of 1.72 g of 10% palladium on charcoal. After the hydrogen uptake ceased (940 ml) the catalyst was removed by filtration and the solvent was evaporated to give 3.90 g (94%) of pure 14. Sublimation [125°

(25) This ketone was identified by a spectral and chromatographic comparison with an authentic sample of 12 prepared by hydrogenation of 1.[2]

(26) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1968, p 1292.

(0.4 mm)] gave an analytical sample, mp 139–140°. The ir spectrum showed peaks at 1710 and 800 cm^{-1}. The nmr spectrum showed peaks at τ 5.50–5.80 (m, H-4_{exo}, J = 4.2, 6.4 Hz), 6.18 (dd, H-3_{endo}, J = 4.0, 2.4 Hz), 6.70–7.70 (m, H-1, H-2, H-5, H-6, H-12a), 7.80–8.20 (m, H-7–H-10, H-12s).

Anal. Calcd for $C_{12}H_{16}Cl_2O$: C, 58.31; H, 6.53; Cl, 28.69. Found: C, 58.55; H, 6.50; Cl, 28.50.

Tricyclo[4.4.1.$1^{2,5}$]dodec-3-en-11-one (4).—A mixture of 3.90 g of 14, 2.0 g of zinc chloride, and 21.3 g of zinc dust in 215 ml of 95% ethanol was refluxed at 100° for 25 hr. The mixture was allowed to cool to room temperature, the gray solid was filtered off, and the ethanol solution was diluted with ether. The ether was washed twice with water and the water was back extracted twice with ether. The combined ether fractions were dried over magnesium sulfate, the drying agent was filtered off, and the ether was evaporated. Purification of the resulting crystals by sublimation [100° (12 mm)] yielded 2.52 g (91%) of pure 4 identical in all respects with a sample prepared from deoxygenation of 3 (*vide supra*).

Catalytic Hydrogenation of Tricyclo[4.4.1.$1^{2,5}$]dodec-3-en-11-one (4).—A solution of 48 mg of 4 in 3 ml of 95% ethanol was exposed to hydrogen gas in the presence of 35 mg of 10% palladium on charcoal. After 25 min the uptake ceased; no additional hydrogen was taken up over the next 15 min. The solution was filtered and the solvent was evaporated to give 48 mg (98%) of pure colorless 12.[25] The nmr spectrum showed only a complex multiplet between τ 7.2 and 8.9.

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The Isomerization of Tri-*tert*-butylcyclopropenyl Azide[1]

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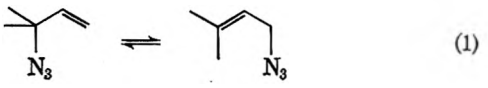
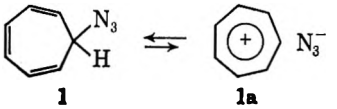
Tri-*tert*-butylcyclopropenyl azide has been synthesized by the reaction of tri-*tert*-butylcyclopropenyl perchlorate or fluoroborate with sodium azide. The nmr spectra exhibited both solvent and temperature dependence as the result of chemical exchange of the azide function between three equivalent annular sites. Total line shape analyses of the spectra provided activation parameters in six widely different solvents. The sensitivity of the degenerate isomerization rate to the nature of the solvent suggests that the process proceeds *via* an ionization–recombination (ion-pair) mechanism.

In recent years much interest has been devoted to the problem of structure and reactivity of organic azides.[2] The rates of rearrangement of allylic azides (eq 1) have been shown to be relatively insensitive to



(1)

alkyl substitution and changes in solvent polarity.[3] These results are consistent with a concerted mechanism involving a [3,3] sigmatropic shift. On the other hand, Wulfman, *et al.*,[4] have suggested that the temperature and solvent dependence of the nmr spectrum of tropyl azide (1) can be rationalized on the basis of a mechanism involving ionization to the tropylium ion–azide ion pair (1a). Upon warming a



1 1a

solution of 1 in acetone-d_6 at −35 to −15°, all nmr (60 MHz) spin–spin splitting disappears, whereas, at 30°, all chemical shifts are indistinguishable and the spectrum exhibits a single broad maximum. The position of the center of gravity of the spectrum at −35°, namely δ 5.85, is identical with the corresponding position at 52° but is much further upfield than the tropylium ion resonance (δ 10.0). The independence of the spectra of concentration provided evidence that the protons in tropyl azide approach equivalency *via* an intramolecular degenerate isomerization process. However, it was shown that 1 in the presence of added tropylium perchlorate exhibits spectra ranging from those showing a single sharp line between tropylium ion and exchanging azide peaks, through those showing broad absorption in the same region, to those showing separate peaks. Furthermore, it was reported that under certain conditions these spectra show extreme concentration dependence attributed to an intermolecular exchange process between tropyl azide and tropylium perchlorate *via* an ion triplet 2.

$$C_7H_7^+ \quad N_3^- \quad C_7H_7^+$$
2

Since cyclopropenyl azides are ($4n$ + 2) vinylogs of tropyl azide (1), it was of interest to establish whether they revealed in their nmr spectra any of the unusual features exhibited by 1. However, it has been reported that the reaction of triphenylcyclopropenyl bromide with sodium azide in DMF gives the unstable covalent triphenylcyclopropenyl azide (3) which undergoes facile rearrangement to the *v*-triazine 4.[5,6]

(1) A preliminary communication of this work has appeared in which a different total line shape analysis (TLS) program was employed: R. Curci, V. Lucchini, P. J. Kocienski, G. T. Evans, and J. Ciabattoni, *Tetrahedron Lett.*, 3293 (1972).

(2) E. Lieber, J. S. Curtice, and C. N. R. Rao, *Chem. Ind. (London)*, 586 (1966).

(3) A. Gagneux, S. Winstein, and W. G. Young, *J. Amer. Chem. Soc.*, **82**, 5956 (1960).

(4) (a) C. E. Wulfman, C. F. Yarnell, and D. S. Wulfman, *Chem. Ind. (London)*, 1440 (1960); (b) D. S. Wulfman, L. Durham, and C. E. Wulfman, *ibid.*, 859 (1962); (c) D. S. Wulfman and J. J. Ward, *Chem. Commun.*, 276 (1967); (d) D. S. Wulfman, Ph.D. Thesis, Stanford University, 1962.

(5) E. A. Chandross and G. Smolinsky, *Tetrahedron Lett.*, 19 (1960).

(6) I. A. D'yakanov and R. R. Kostikov, *Russ. Chem. Rev.*, **36**, 557 (1967).

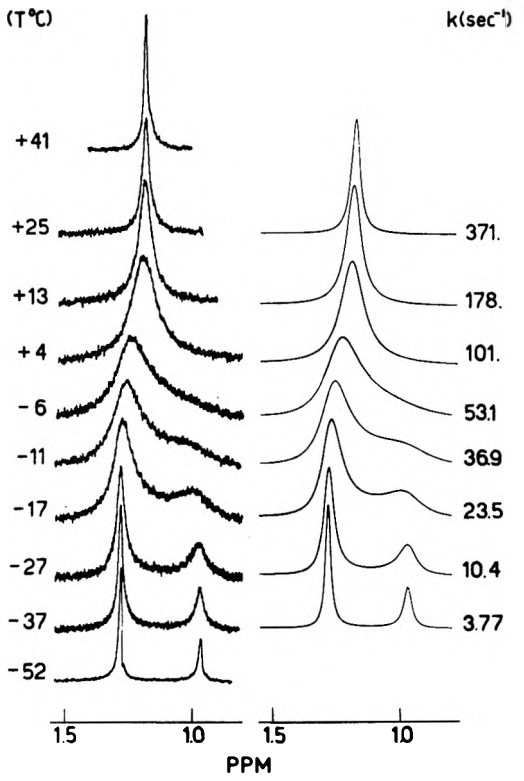
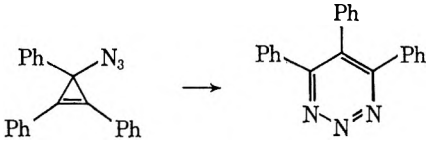


Figure 1.—Experimental (left) and computer-calculated (right) nmr spectra (90 MHz) of tri-*tert*-butylcyclopropenyl azide (0.08 *M*) in acetone-d_6 at various temperatures.

Nevertheless, the tendency of trialkylcyclopropenyl azides such as tri-*tert*-butylcyclopropenyl azide (**6**) toward ionization is *a priori* expected to be increased relative to **3**, since the tri-*tert*-butylcyclopropenyl

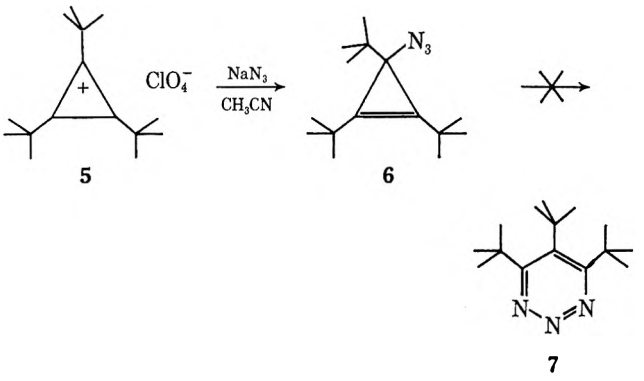


3 **4**

cation (pK_{R^+} = 6.5 in 50% H_2O–CH_3CN)[7] is considerably more stable than the corresponding triphenyl derivative (pK_{R^+} = 3.1 in 50% H_2O–CH_3CN).[8] Tri-*tert*-butylcyclopropenyl azide was selected on the basis of the above reasoning as well as the fact that it would be expected to exhibit a simple nmr spectrum.

Results and Discussion

Reaction of tri-*tert*-butylcyclopropenyl fluoroborate[9] or perchlorate[10] (**5**) with sodium azide in acetonitrile at 0° followed by aqueous work-up afforded tri-*tert*-butylcyclopropenyl azide (**6**) in nearly quantitative yield as a stable, colorless oil which could be distilled under reduced pressure. Azide **6** has been stored neat in the crystalline state at about −10° (mp *ca.* 2°) for periods exceeding 6 months with no detectable decomposition. Unlike **3** no evidence was found for the rearrangement of **6** to *v*-triazine **7**. The infrared, ultraviolet, and nmr spectra were consistent with the covalent formulation **6**. In the infrared (CCl_4) **6** exhibited strong characteristic azide absorption at 2085 cm^{-1} and weak cyclopropene (C=C) absorption at 1810 cm^{-1}.[11] The ultraviolet spectrum (cyclohexane) showed the characteristic azide maximum at 295 nm (ϵ 28).[12] The nmr spectrum exhibited a symmetrical exchange-broadened singlet at δ 1.21 (60 MHz, $W_{1/2}$ = 9 Hz). The appearance of solution spectra was a function of solvent and temperature and in acetone-d_6 (0.08 *M*) varied from two sharp singlets (−52°, 90 MHz, $W_{1/2}$ = 1.2 Hz) at δ 1.28 and 0.96 in a 2:1 ratio, respectively, to one singlet (41°, 90 MHz, $W_{1/2}$ = 1.2 Hz) at δ 1.19 (approximate weighted average position). By comparison the completely ionic tri-*tert*-butylcyclopropenyl perchlorate or fluoroborate exhibits a sharp singlet at δ 1.58 in $CDCl_3$. Although the mass spectrum of **6** did not reveal a parent ion, an intense peak at *m/e* 207 (M − 42) was observed corresponding to the cyclopropenyl cation. The lability of the azide was demonstrated by the reaction of a solution of **6** in ethanol with aqueous silver nitrate, affording an immediate white precipitate of silver azide. Furthermore, a solution of the cyclopropenyl azide **6** in acetonitrile reacted slowly with potassium cyanide to give the corresponding tri-*tert*-butylcyclopropenyl nitrile in 80% yield. This nitrile proved to be identical in all respects with an authentic sample prepared by the reaction of tri-*tert*-butylcyclopropenyl perchlorate with potassium cyanide.



5 **6** **7**

The nmr spectra of **6** were recorded in a series of solvents of widely different characteristics at various temperatures. At sufficiently low temperatures the spectrum consisted of two sharp singlets of relative intensity 2:1. However, as the temperature was increased, the two peaks broadened, coalesced, and finally merged into one sharp peak whose position approximated the weighted-average position of the two singlets at low temperature (see Figure 1). This nmr behavior suggests that **6** is in equilibrium among its three congruent isomers.[13] Chemical shift data of azide **6** as well as the ionic tri-*tert*-butylcyclopropenyl perchlorate (**5**) in a series of solvents are presented in Table I.

In order to obtain rates and activation parameters for the apparent degenerate isomerization process in which the *tert*-butyl groups become magnetically equivalent, the spectra in six representative solvents were subjected to a total line shape analysis (TLS).

(7) J. Ciabattoni and E. C. Nathan, *Tetrahedron Lett.*, 4997 (1969).
(8) R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, **83**, 2367 (1961).
(9) J. Ciabattoni, E. C. Nathan, A. E. Feiring, and P. J. Kocienski, *Org. Syn.*, in press.
(10) J. Ciabattoni and E. C. Nathan, *J. Amer. Chem. Soc.*, **91**, 4766 (1969).
(11) G. L. Closs, *Advan. Alicycl. Chem.*, **1**, 53 (1966).
(12) W. D. Closson and H. B. Gray, *J. Amer. Chem. Soc.*, **85**, 290 (1963).
(13) R. Breslow, G. Ryan, and J. T. Groves, *J. Amer. Chem. Soc.*, **92**, 988 (1970).

TABLE I

POSITIONS OF NMR ABSORPTION OF TRI-*tert*-BUTYLCYCLOPROPENYL AZIDE AND TRI-*tert*-BUTYLCYCLOPROPENYL PERCHLORATE IN VARIOUS SOLVENTS

Solvent	Azide 6[a]	Cation 5[a]	Temp, °C	Dielectric constant[b]
Neat	1.21		40	
	1.18		75	
CCl_4	1.18		70	2.24
	0.92 (9 H), 1.27 (18 H)		−35	
$CDCl_3$	1.17	1.58	40	4.81
	0.95 (9 H), 1.27 (18 H)		−65	
CD_2Cl_2	1.17	1.58	40	9.08
Acetone-d_6	1.19	1.62	40	20.7
	0.96 (9 H), 1.28 (18 H)	1.62	−40	
CD_3OD	1.18		40	32.6
	0.95 (9 H), 1.26 (18 H)		−65	
CD_3NO_2	1.19	1.60	40	35.8[c]
DMF-d_7	1.17	1.54	40	37.6[d]
	0.95 (9 H), 1.26 (18 H)		−60	
CD_3CN	1.18	1.51	40	37.5
	0.96 (9 H)[e], 1.28 (18 H)[e]		−40	
Ethylene carbonate	1.16	1.56	40	95.0
SO_2 (liquid)	1.58	1.58	−42	14.1

[a] All positions are given in units of δ to ±0.01 ppm. [b] Dielectric constants for undeuterated solvents at 20° except as noted. [c] At 30°. [d] At 25°. [e] Estimated values from spectra at −40°.

The line shapes were computer-calculated employing Binsch's DNMR program[14a] and rate constants were estimated by determining the best fit between experimental and theoretical spectra; in most instances (see Table II) the experimental spectra were fed point by point into the computer and the theoretical curves representing the best fit were found by a least squares method.[14b-d] The results of typical fits are shown in Figure 1. Statistical least squares analyses of Eyring plots provided approximate $\Delta H^{\pm}$ and $\Delta S^{\pm}$ values.[14b] These activation parameters are shown in Table II together with their uncertainties. It should be pointed out, however, that systematic errors may be significantly larger than these estimates.[15] It is apparent from Table II that no significant changes in the activation parameters were found on changing the cyclopropenyl azide concentration, consistent with an *intramolecular* rather than an intermolecular exchange process.

The effect of added salts was also investigated. The addition of 0.07 *M* lithium perchlorate to a solution of **6** in acetone-d_6 resulted in a decrease in the coalescence temperature and an increase in rate at 25°. Similarly, the addition of 0.05 *M* tri-*tert*-butylcyclopropenyl perchlorate (**5**) resulted in the observation of a positive salt effect (see Table II). On the other hand, when an equimolar quantity of **5** was added to a solution of **6** in CD_3CN or CD_3NO_2 at 40°, only a single sharp peak was observed halfway between the singlet for pure cation and the singlet for pure azide. The results suggest that in these polar solvents there is rapid intermolecular exchange of the azide function between **5** and **6** in analogy with the tropyl azide–tropylium perchlorate system (*vide supra*). However, the temperature-dependent nmr spectrum of **6** in the presence of **5** in acetone-d_6 (Figure 2) reveals that the above intermolecular azide group exchange actually occurs between the cation and the dynamic tri-*tert*-butylcyclopropenyl azide molecule, which is already undergoing a fast intramolecular isomerization process on the nmr time scale.

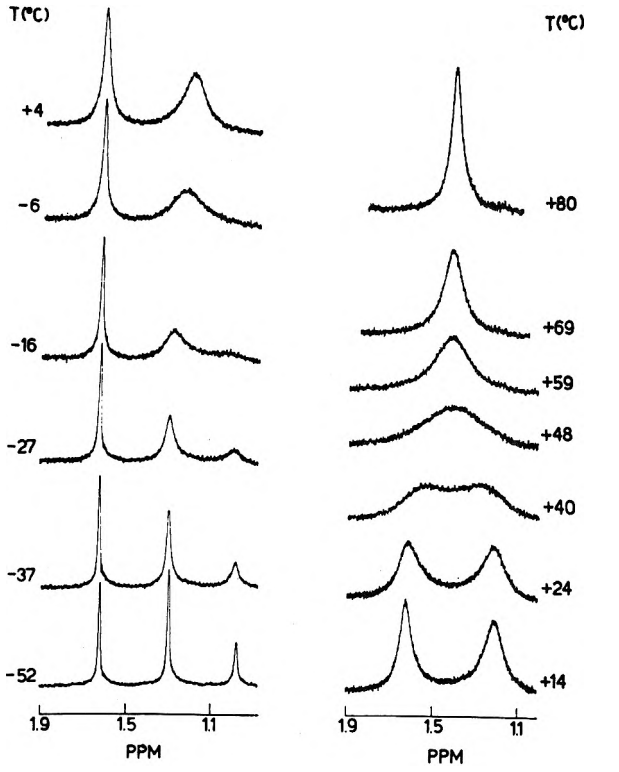


Figure 2.—The nmr spectra (90 MHz) of tri-*tert*-butylcyclopropenyl azide (0.08 *M*) in the presence of tri-*tert*-butylcyclopropenyl perchlorate (0.05 *M*) in acetone-d_6 at various temperatures.

It can be seen from Table II that the rate of intramolecular isomerization of **6**, like that of **1**, is very sensitive to the nature of the solvent in contrast with the analogous rearrangement of allylic azides.[3] The observed solvent effects, instead, are consistent with an ionic process involving the ionization of **6** to an ion pair **6a**[16] as depicted in Scheme I (path a). However, the concurrent intervention of a concerted pathway b cannot be excluded on the basis of our data. A concerted [1,3] sigmatropic shift is of course forbidden but a [$_{\omega}2 + {}_{\pi}2 + {}_{\sigma}2$] process and a [3,3] sigmatropic shift represent possible allowed processes.[17]

Inspection of the data in Table I does not reveal any significant solvent effect on the single resonance position of **6**, which in every case, with the exception of SO_2, was about 0.4 ppm upfield from the signal of cation **5**. This suggests that the position of equi-

(14) (a) G. Binsch, *J. Amer. Chem. Soc.*, **91**, 1304 (1969); (b) G. Binsch, *Top. Stereochem.*, **3**, 97 (1968); (c) R. R. Shoup, E. D. Becker, and M. L. McNeel, *J. Phys. Chem.*, **76**, 71 (1972); (d) L. G. Sillen, *Acta Chem. Scand.*, **18**, 1085 (1964), and references cited therein.

(15) B. L. Hawkins, W. Bremser, S. Borcic, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 4472 (1971).

(16) A more elaborate scheme would include a solvent-separated ion pair and dissociated ions depicting various degrees of association between the azide ion and cyclopropenyl cation.

(17) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.

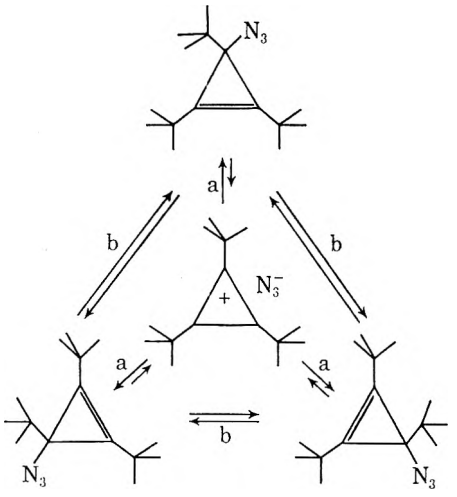
TABLE II

ACTIVATION PARAMETERS[a] AND RELATIVE RATES FOR THE ISOMERIZATION OF 6 IN VARIOUS SOLVENTS

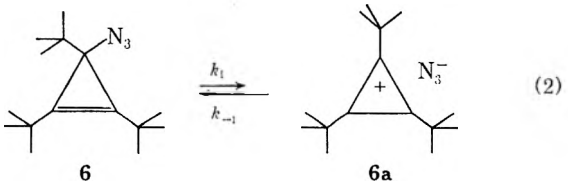
Solvent	Dielectric constant	Azide, M	$\Delta H^{\pm}$ [b]	$\Delta S^{\pm}$ [c]	$\Delta G^{\pm}_{25°}$ [b]	Relative rates (25°)[d]	T_c, °C[e]
Acetone-d_6	20.7	0.02	10.7 ± 0.3	−10.4 ± 1	13.8 ± 0.4		−2.5
		0.06	10.7 ± 0.2	−10.8 ± 0.5	13.9 ± 0.2	0.95×10^2	−1.5
		0.08	10.0 ± 0.2	−13.6 ± 0.5	14.0 ± 0.2		−2.5
		0.14	10.4 ± 0.2	−11.6 ± 0.5	13.9 ± 0.2		−2.5
		0.29	10.7 ± 0.3	−10.7 ± 0.5	13.9 ± 0.3		−1.0
Acetone-d_6, 0.05 M **5**		0.08	11.5 ± 0.3	−6.6 ± 0.5	13.5 ± 0.3	1.9×10^2	−8.5
Acetone-d_6, 0.07 M $LiClO_4$		0.08	9.8 ± 0.2	−12.5 ± 0.5	13.5 ± 0.2	1.9×10^2	−11.0
CCl_4	2.24	0.02	13.3 ± 0.3	−10.8 ± 0.5	16.5 ± 0.3		62.5
		0.10	13.1 ± 0.3	−11.5 ± 0.5	16.5 ± 0.3		63.5
		0.19	13.7 ± 0.3	−9.6 ± 0.5	16.6 ± 0.3	1	63.5
$CDCl_3$	4.81	0.12	7.8 ± 0.1	−17.6 ± 0.5	13.0 ± 0.1	4.4×10^2	−31.5
DMF-d_7	37.6	0.10	10.4 ± 0.2	−10.0 ± 0.5	13.4 ± 0.2	2.2×10^2	−18.0
CD_3CN	37.5	0.31	7.8 ± 0.3	−17.4 ± 0.5	13.0 ± 0.3	4.4×10^2	−31.5
CD_3OD	32.6	0.09	10.6 ± 0.2	−4.8 ± 0.5	12.0 ± 0.2	2.4×10^3	−38.0

[a] Calculated from rate data obtained by a computer-determined point by point fit of experimental to theoretical spectra at various temperatures. Uncertainties arise from statistical analysis of random errors. Any systematic errors could result in much larger errors in the derived parameters; this might be particularly true for activation parameters estimated for the intramolecular isomerization process in the presence of added **5** (sixth entry) because of some contribution from the intermolecular exchange process (see text and Figure 2). [b] kcal mol^{-1}. [c] cal deg^{-1} mol^{-1}. [d] ±10%. [e] Coalescence temperature (90 MHz).

SCHEME I



librium between **6** and **6a** must lie almost entirely in favor of the covalent form (eq 2). In liquid SO_2



(2)

at −42°, however, the chemical shift of the azide was identical with that of **5** (δ 1.58), demonstrating that in this solvent **6** exists as a completely ionized species. This is not surprising in view of the well-documented ability of SO_2 to complex strongly with inorganic anions, forming monosolvates.[18]

From the data in Table II it is evident that there is no simple correlation between the dielectric constant of the solvent and activation parameters or relative rates, although with the exception of chloroform, which exhibits a higher rate than expected, a rough trend does exist between the log of the rates and Kosower's Z values.[19] The observed order of relative rates apparently reflects, at least in part, specific solvation interactions. The high rate in $CDCl_3$ could be attributed to hydrogen bonding to the azide function.[20] This effect may also contribute to the fast rate observed in methanol relative to the rates in aprotic solvents of comparable dielectric constant such as DMF and acetonitrile (Table II). It can also be seen that the $\Delta S^{\pm}$ value in methanol is significantly less negative than that found in DMF and acetonitrile. This appears to be consistent with the ionic path a (Scheme I), since the separation of opposite charges in going from covalent azide to transition state should require less reorganization of methanol molecules than the molecules of aprotic solvents.[20,21] Furthermore, the positive salt effects observed in acetone-d_6 are consistent with a process involving ionization in poorly ionizing media.[22]

After this work was completed, a brief paper by Closs and Harrison appeared describing a similar nmr study of trimethylcyclopropenyl azide.[23] Our results are in substantial agreement with those reported by these authors, who also suggested an ionic pathway for the isomerization. It should be mentioned, however, that tri-*tert*-butylcyclopropenyl azide, in contrast with trimethylcyclopropenyl azide, does not exhibit rearrangement to a *v*-triazine in competition with the degenerate isomerization process.[23]

(18) (a) E. J. Woodhouse and T. H. Norris, *Inorg. Chem.*, **10**, 614 (1971); (b) G. Illuminati, *Rend. Accad. Naz. Lincei*, **11**, 303 (1968); (c) T. C. Waddington, "Non-Aqueous Solvent Systems," Academic Press, New York, N. Y., 1965, pp 256–259.

(19) (a) E. M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N. Y., 1968, p 293 ff; (b) R. W. Alder, R. Baker, and J. M. Brown, "Mechanism in Organic Chemistry," Wiley-Interscience, London, 1971, p 40 ff.

(20) C. D. Ritchie, *Accounts Chem. Res.*, **5**, 348 (1972), and references cited therein.

(21) (a) R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Broxton, *J. Amer. Chem. Soc.*, **90**, 5049 (1968); (b) P. Haberfield, L. Clayman, and J. S. Cooper, *ibid.*, **91**, 787 (1969).

(22) (a) S. Winstein, S. Smith, and D. Darwish, *J. Amer. Chem. Soc.*, **81**, 5511 (1959); (b) A. Iliceto, A. Fava, U. Mazzucato, and O. Rossetto, *ibid.*, **83**, 2729 (1961), and references cited therein; (c) R. A. Sneen and W. A. Bradley, *ibid.*, **94**, 6975 (1972), and references cited therein.

(23) G. L. Closs and A. M. Harrison, *J. Org. Chem.*, **37**, 1051 (1972).

Experimental Section

Melting points are uncorrected. High-purity commercial solvents were employed for all spectral determinations. Infrared and ultraviolet spectra were recorded with a Perkin-Elmer Model 337 and a Cary Model 14 recording spectrophotometer, respectively. Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer. The nmr spectra were recorded on a Bruker HFX-10 (90 MHz) or a Varian A-60A (60 MHz) instrument with variable-temperature capability. Line shapes were calculated by a CDC-6600 computer using the DNMR program developed by Binsch.[14] The rate-dependent *tert*-butyl resonances of 6 were simulated for the azide moiety exchanging among three equivalent sites. High-quality experimental spectra were obtained on the Bruker HFX-10 instrument by constantly checking the field homogeneity with an internal standard. The same scale (2.00 Hz/cm) was employed for both the experimental and computer-simulated spectra. Sample temperatures were determined by the chemical shift method employing a capillary containing methanol (or ethylene glycol) which was inserted into the sample tube. Reference to revised calibration curves provided the temperatures.[14c,24]

1,2,3-Tri-*tert*-butyl-3-azidocyclopropene (6).—To a solution of 1.00 g (3.28 mmol) of tri-*tert*-butylcyclopropenyl perchlorate in 10 ml of acetonitrile was added 0.228 g (3.51 mmol) of sodium azide (Matheson Coleman and Bell) in one portion. The mixture was stirred at 0° for 1 hr, after which dilution with 50 ml of water resulted in the separation of a colorless oil. The oil was then extracted into two 15-ml portions of ether. After the ether layer was washed with five 10-ml portions of water and dried over anhydrous magnesium sulfate, the solvent was removed *in vacuo* to afford the cyclopropenyl azide (0.815 g, 100%) as a colorless oil which crystallized upon refrigeration. Azide 6 is quite stable and has been stored neat in the crystalline state at about −10° for periods exceeding 6 months with no detectable decomposition. Purification, if necessary, may be effected by short-path distillation, pot temperature 40–50° (0.03–0.05 mm): mp ~2°; ν_{max} (CCl_4) 2950 (s), 2900 (m), 2870 (m), 2085 (vs), 1810 (w), 1475 (m), 1455 (m), 1390 (m), 1365 (m), 1258 (m), and 910 cm^{-1} (m); λ_{max} (cyclohexane) 295 nm (ϵ 28); mass spectrum *m/e* (rel intensity) 207 (33), 206 (11), 166 (23), 150 (16), 123 (68), 108 (10), 95 (18), 93 (10), 82 (10), 81 (15), 69 (18), 68 (15), 67 (23), 57 (100), 56 (10), 55 (23), 53 (12), 43 (27), 42 (38), 41 (29), and 39 (19).

Anal. Calcd for $C_{15}H_{27}N_3$: C, 72.24; H 10.91; N 16.85; mol wt, 249. Found: C, 72.36; H, 10.96; N, 16.74; mol wt, 250 (osmometric, CCl_4).

Reaction of azide 6 with potassium cyanide in aqueous acetonitrile followed by work-up as described above gave 1,2,3-tri-*tert*-butyl-3-cyanocyclopropene (80%), which was identical in all respects with an authentic sample prepared by the reaction of cation 5 with potassium cyanide: mp 30–31°; ν_{max} (CCl_4) 2970 (s), 2900 (m), 2870 (m), 2210 (m), 1845 (w), 1610 (w), 1475 (m), 1455 (m), 1380 (m), 1365 (m), and 1040 cm^{-1} (m); nmr (CCl_4) δ 1.00 (9 H, s) and 1.27 (18 H, s); mass spectrum *m/e* (rel intensity) 233 (4), 176 (100), 162 (13), 150 (19), 135 (12), 57 (72), and 41 (40).

Acknowledgments.—We thank the Italian National Research Council (C. N. R., Rome) and the Research Corporation for financial support of this research. We are also grateful to the Committee on International Exchange of Persons (Washington, D. C.) for a Senior Fulbright-Hays grant to J. C. (1972–1973) and for a travel grant to R. C. (summer, 1971).

Registry No.—5, 19985-80-9; 6, 38409-72-2; 1,2,3-Tri-*tert*-butyl-3-cyanocyclopropene, 40893-42-3.

(24) (a) A. L. Van Geet, *Anal. Chem.*, **42**, 679 (1970); (b) *ibid.*, **40**, 2227 (1968).

Substituent Effects in the Ring Expansion Reactions of Isopropenylcycloalkanols by *tert*-Butyl Hypochlorite

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1-Isopropenylcyclobutanol was prepared by the conventional Grignard method. 1-Isopropenylcyclopropanol was synthesized by the addition of isopropenylmagnesium bromide to 1,3-dichloroacetone followed by ferric chloride induced coupling. The cyclobutanol underwent the chlorinative ring expansion with *tert*-butyl hypochlorite to produce 2-methyl-2-(chloromethyl)cyclopentanone in 81% yield. The cyclopropanol proved to be so labile that it spontaneously rearranged to 2,2-dimethylcyclobutanone. The acid-catalyzed ring expansion of 1-isopropenylcyclobutanol was accomplished with sulfuric acid in the presence of 2,4-dinitrophenylhydrazine. A slight preference for phenyl migration over methylene migration (60:40) was demonstrated in the reaction of 1-isopropenyl-1-indanol with *tert*-butyl hypochlorite. The substituent effect studies were extended to *trans*-1-isopropenyl-2-methylcyclopentan-1-ol and *exo*-2-isopropenylnorbornan-2-ol. Structure assignments for the ring expansion products from these two substrates were based on an nmr study. Methine carbon migration was shown to predominate over methylene carbon migration. These results were rationalized in terms of a nonconcerted mechanism with some carbonium-ion character in the transition state. The observed stereochemistry of the product ketones was explained on the basis of the conformational preference of the isopropenyl group in the reactant alcohol.

Part A

Carbocyclic ring expansion is a useful synthetic trick of the organic chemist.[1] Some of the classical methods applied to ring homologation by one carbon atom are the Demjanov[2] rearrangement, the Tiffeneau–Demjanov[2] rearrangement, and the pinacol[3] rearrangement. Well-known ring homologation methods which incorporate a heteroatom into the ring are the Baeyer–Villiger reaction (oxygen)[4] and the Beckmann rearrangement (nitrogen).[5] Several years ago we discovered a chlorinative ring-expansion reaction which homologates a ring by one carbon atom (eq 1).[6] This

(1) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968.

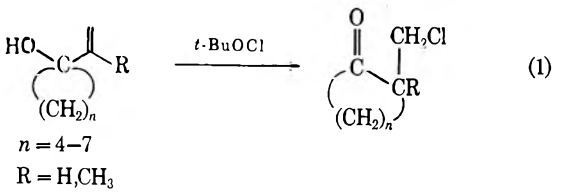
(2) P. A. Smith and D. R. Baer, "Organic Reactions," Vol. 11, Wiley, New York, N. Y., 1960, p 157.

(3) Y. Pocker in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Wiley, New York, N. Y., 1964, p 1.

(4) C. H. Hassall, "Organic Reactions," Vol. 9, Wiley, New York, N. Y., 1957, p 73.

(5) L. G. Donaruma and W. Z. Heldt, "Organic Reactions," Vol. 11, Wiley, New York, N. Y., 1960, p 1.

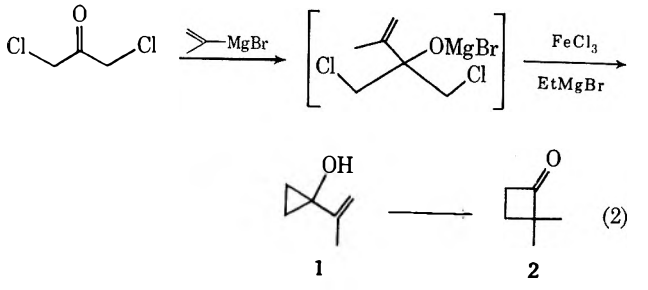
(6) C. R. Johnson, C. J. Cheer, and D. Goldsmith, *J. Org. Chem.*, **29**, 3320 (1964).



(1)

paper reports an investigation of the ring expansion of the smaller ring alcohols (eq 1, n = 2, 3) and a study of substituent effects and stereochemistry.

The synthesis of 1-isopropenylcyclopropanol was undertaken with the awareness that 1-vinylcyclopropanols were an unreported class of compound at the time, although several methods were available for the synthesis of 1-alkyl- and 1-arylcyclopropanols.[7] Reaction of 1,3-dichloroacetone with isopropenylmagnesium bromide, followed by addition of ferric chloride and ethylmagnesium bromide[8] and subsequent hydrolysis, gave, after removal of the solvent under vacuum and flash distillation under 20°, a 15% yield of a 4:1 mixture of 1-isopropenylcyclopropanol and 2,2-dimethylcyclobutanone (eq 2). Upon standing for 1



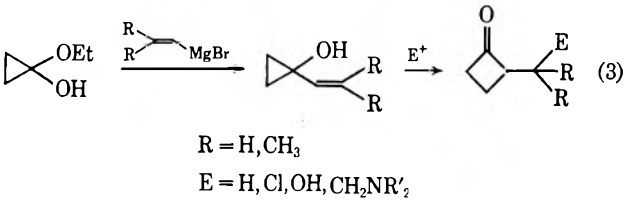
(2)

day at room temperature, either neat or in solution, the rearrangement of **1** to **2** was complete.

Reaction of the mixture of 1-isopropenylcyclopropanol and 2,2-dimethylcyclobutanone with *tert*-butyl hypochlorite resulted in a complex mixture of products, apparently owing to chlorination of 2,2-dimethylcyclobutanone competing with chlorinative ring expansion of the cyclopropanol. Although chlorinative ring expansion did occur, owing to the lack of synthetic utility of the reaction, the product was not rigorously characterized.

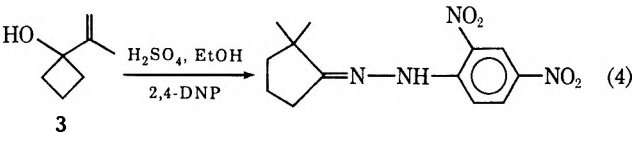
Several related vinylcyclopropanols have recently been reported. Wasserman and Clagett synthesized 1-cyclopentadienylcyclopropanol and found that it also undergoes a facile acid-catalyzed ring expansion.[9] Konzelman and Conley have reported isolating 1-vinylcyclopropanol as a minor product from the deamination of spiropentylamine.[10] Wasserman and coworkers have reported on the synthesis of two vinylcyclopropanols and their ring-expansion reactions with a variety of electrophilic reagents (eq 3).[11]

Attention was next focused on the cyclobutanol system. The synthesis of 1-isopropenylcyclobutanol was accomplished in 61% yield by Grignard addition to cyclobutanone. Because of the facility with which 1-



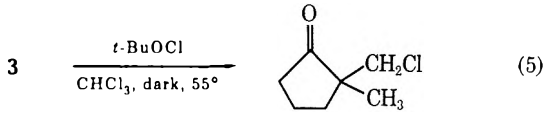
(3)

isopropenylcyclopropanol underwent acid-catalyzed ring expansion, efforts were made to bring about a similar reaction with isopropenylcyclobutanol. A variety of acids and solvents were examined with no success. No volatile ketonic product could be detected and dark, tarry residues resulted in most cases. However, a solution of 1-isopropenylcyclobutanol in ethanol and sulfuric acid in the presence of 2,4-dinitrophenylhydrazine resulted in a 51% yield of the hydrazone of 2,2-dimethylcyclopentanone (eq 4). When a similar



(4)

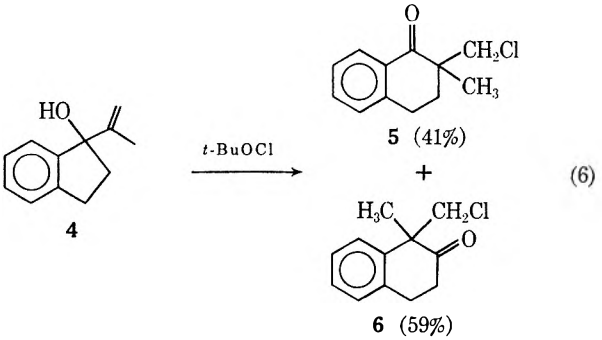
reaction was attempted with 1-isopropenylcyclopentanol, a dark solution resulted with no evidence of hydrazone formation. The reaction of 1-isopropenylcyclobutanol with *tert*-butyl hypochlorite resulted in an 81% yield of 2-(chloromethyl)-2-methylcyclopentanone (eq 5).



(5)

A study of substituent effects in the chlorinative ring expansion of 1-vinylcycloalkanols was initiated with the 1-indanol system. The synthesis of 1-isopropenyl-1-indanol (**4**) was accomplished in 38% yield by the Grignard reaction on 1-indanone.

The usual procedure[6] for the chlorinative ring expansion on 1-isopropenyl-1-indanol resulted in an 88% yield of product consisting of two isomers (eq 6). The



(6)

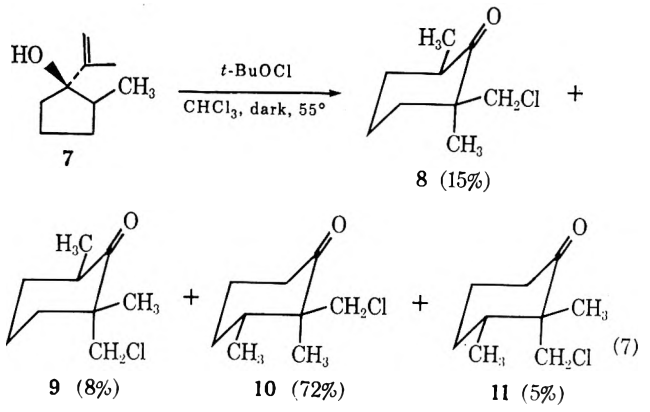
isomers were separated and collected by glc and identified through their infrared and nmr spectra. The first isomer eluted exhibited a carbonyl band at 1680 cm^{-1} and was assigned the 1-tetralone structure **5**. The second isomer showed a carbonyl band at 1720 cm^{-1} and was assigned the 2-tetralone structure **6**.

Alcohol **7** was prepared by the addition of isopropenylmagnesium bromide to 2-methylcyclopentanone. The Grignard reaction was accomplished in 28% yield, although the actual yield based on consumed starting

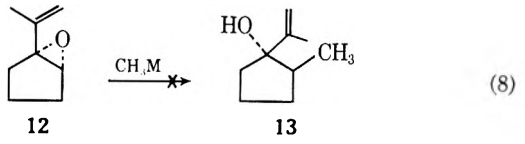
(7) C. H. DePuy, *Trans. N. Y. Acad. Sci., Ser. II*, **28**, 561 (1966).
(8) C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964).
(9) H. H. Wasserman and D. C. Clagett, *J. Amer. Chem. Soc.*, **88**, 5368 (1966).
(10) L. M. Konzelman and R. T. Conley, *J. Org. Chem.*, **33**, 3828 (1968).
(11) H. H. Wasserman, R. E. Cochoy, and M. S. Baird, *J. Amer. Chem. Soc.*, **91**, 2375 (1969).

material would be higher since a considerable amount of 2-methylcyclopentanone was recovered. Two isomers are theoretically possible from the Grignard addition, but glc analysis with several columns under varying conditions showed only one peak. Literature data on related reactions supports the structure **7** having trans alkyl groups.[12]

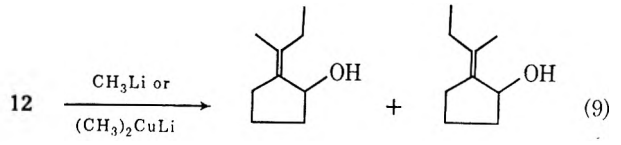
Following reaction of the alcohol **7** with *tert*-butyl hypochlorite and removal of the solvent, the infrared spectrum of the crude product showed a strong carbonyl band at 1720 cm^{-1}. Glc analysis showed the presence of four isomers in the ratio 15:8:72:5 (eq 7).



A key step in one scheme planned for the synthesis of *cis*-1-isopropenyl-2-methylcyclopentan-1-ol (**13**) was the addition of an organometallic reagent to the oxirane moiety of 1-isopropenyl-1,2-epoxycyclopentane (**12**) (eq 8). Neither the addition of methyllithium or

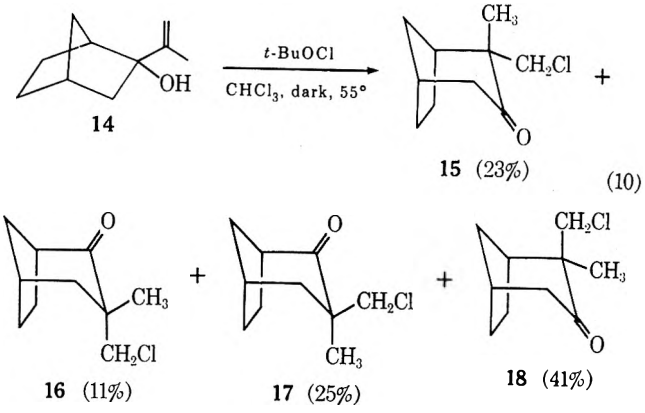


lithium dimethylcuprate yielded the desired product, but rather gave a mixture of isomeric alcohols resulting from conjugate addition (eq 9). The facile reac-



tion observed in this case with the cuprate initiated our interest in exploring the general reactions of cuprates and epoxides.

The reaction of isopropenylmagnesium bromide with bicyclo[2.2.1]heptan-2-one gave 2-isopropenylbicyclo[2.2.1]heptan-2-ol (2-isopropenylnorbornan-2-ol) (**14**) in 82% yield. Only one isomer could be detected by glc analysis. The product was assigned the exo-alkyl configuration by analogy with the addition of methylmagnesium iodide to 2-norbornanone, where 95% of the *exo*-2-methylnorbornan-2-ol was obtained.[13] When subjected to the chlorinative ring expansion reaction, *exo*-2-isopropenylnorbornan-2-ol (**14**) gave a mixture of four isomeric ketones (eq 10).



In the chlorinative ring expansion of **4** it is observed that phenyl migration is slightly preferred over methylene, and in the ring expansions of **7** and **14** it is found that methine migration is preferred to methylene. These observations are consistent with rearrangements involving carbonium ion intermediates. Migratory preferences involving cyclic systems never tend to be as clear-cut as those involving acyclic systems because of the arrogation of electronic factors by steric effects.[1]

Part B

Structural Assignments by Nmr Studies.—Aromatic solvent induced shifts (ASIS) in nmr spectra have been documented for many different classes of compounds.[14] Ketones, and in particular methyl-substituted cyclohexanones, have been studied extensively. The empirical generalization of Connolly and McCrindle for predicting the direction and magnitude of benzene-induced solvent shifts[14,15] was especially useful. This rule states that, if a reference plane (P) is drawn through the carbon of the carbonyl group at right angles to the carbon–oxygen bond, then protons close to P show no shift or very small shifts; protons in front of P, *i.e.*, on the same side as the oxygen of the carbonyl group, are deshielded; while protons behind P are shielded. Some data selected from the literature[15,16] on ASIS of methyl-substituted cyclohexanones are summarized as follows.

Methyl substituent	$\Delta^{CDCl_3}_{C_6H_6}$, Hz
2-CH_3 eq	−1.6 to +3.0
2-CH_3 ax	+16.6 to +18.0
3-CH_3 eq	+18.5 to +21.2
3-CH_3 ax	+11.8

Another empirical generalization which has proved useful in distinguishing the axial and equatorial members of isomer pairs is the observation that an axial 2-methyl substituent in a cyclohexanone gives a signal downfield from an equatorial 2-methyl sub-

(12) J. P. Battioni, W. Chodkiewicz, and P. Cadiot, *C. R. Acad. Sci., Ser. C*, **264**, 991 (1967).

(13) N. J. Tiovonen and P. J. Malkonen, *Suom. Kemistilehti*, **32**, 277 (1959).

(14) (a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, pp 104–113, 246; (b) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964.

(15) J. D. Connolly and R. McCrindle, *Chem. Ind. (London)*, 379 (1965).

(16) M. Fetzion, J. Gore, P. Laszlo, and B. Waegell, *J. Org. Chem.*, **31**, 4047 (1966).

stituent in its nmr spectrum run in deuteriochloroform solution.[14b,16,17]

The pertinent nmr data for the four isomers from the ring expanison of **7** necessary for structure assignments based on these two empirical rules are given in Table I. The solvent shift values for the methyl

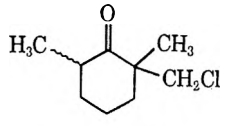
TABLE I

NMR DATA FOR THE CYCLOHEXANONE ISOMERS FROM THE RING EXPANSION OF *trans*-1-ISOPROPENYL-2-METHYLCYCLOPENTAN-1-OL[c,d]

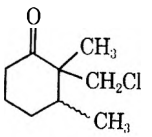
Isomer		ν_{CDCl_3}, Hz	$\nu_{C_6H_6}$, Hz	$\Delta^{CDCl_3}_{C_6H_6}$, Hz[b]
A	CH_3 (d)	61 (J = 6)	55 (J = 6)	6
(15%)	CH_3 (s)	76	53	23
	CH_2Cl[c]	218 (J_{AB} = 0)	212 (J_{AB} = 0)	6
	$\Delta\nu_{AB}$	0	0	
B	CH_3 (d)	62 (J = 6)	57 (J = 6)	5
(8%)	CH_3 (s)	69	65	4
	CH_2Cl	222 (J_{AB} = 11)	194 (J_{AB} = 11)	28
	$\Delta\nu_{AB}$	14	12	
C	CH_3 (d)	55 (J = 6)	36 (J = 7)	19
(72%)	CH_3 (s)	76	65	11
	CH_2Cl	222 (J_{AB} = 11)	210 (J_{AB} = 11)	12
	$\Delta\nu_{AB}$	10	9	
D	CH_3 (d)	57 (J = 6)	36 (J = 6)	21
(5%)	CH_3 (s)	63	37	26
	CH_2Cl	221 (J_{AB} = 11)	207 (J_{AB} = 11)	14
	$\Delta\nu_{AB}$	30	44	

[a] Spectra were run on a 60-MHz instrument (Varian A-60A) with the compounds in 10% w/w solution. [b] The $\Delta^{CDCl_3}_{C_6H_6}$ values for the chloromethyl groups are included in the table, but their significance must be interpreted with caution since $\Delta\nu_{AB}$ is observed to vary with solvent. Although this phenomenon has been observed previously (ref 14a, p 144), the precise solvent effect (if any) on rotamer populations cannot be predicted. [c] The protons of the chloromethyl group in these compounds are chemically nonequivalent (since the methylene group is attached to an asymmetric carbon) and can be magnetically equivalent resulting in an A_2 singlet (isomer A) or magnetically nonequivalent resulting in an AB quartet (isomers B, C, D). [d] Chemical shift values are expressed in hertz downfield from TMS. J's are in hertz.

doublets show unambiguously that A and B are the 6-methyl isomers and that C and D are the 3-methyl isomers.



A and B



C and D

Analysis of the solvent shift data for the methyl singlets (2-CH_3) indicates the following conformational assignments. Interpretation of the chemical-shift data

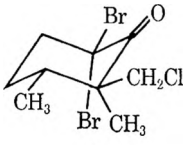
	Isomer	$\Delta^{CDCl_3}_{C_6H_6}$, Hz	2-CH_3 Conformation
6-CH_3	A	23	ax
	B	4	eq
3-CH_3	C	11	eq
	D	26	ax

for the 2-methyl singlets in deuteriochloroform based on the rule that axial methyls appear at lower field than equatorial methyls indicates the following conformational assignments.

	Isomer	ν_{CDCl_3}, Hz	2-CH_3 Conformation
6-CH_3	A	76	ax
	B	69	eq
3-CH_3	C	76	ax
	D	63	eq

Both types of data are in agreement for isomers A and B, which can now be assigned as **8** and **9**, respectively. However, note that the two methods yield contradictory assignments for C and D.

We have solved this dilemma by a study modeled after the work of Wolinsky on the pmr spectra of brominated bicyclooctanes.[18] Wolinsky found that a bromine in 1,3-diaxial relationship to a methyl group will shift the methyl signal about 20 Hz to lower field, while a bromine and methyl in a 1,3-diequatorial relationship cause a much smaller downfield shift (~8 Hz) of the methyl signal. Isomer C was dibrominated and the nmr spectrum of the product was obtained. The 2-methyl singlet of the dibromo ketone occurred at 18 Hz lower field than in C while the chloromethyl experienced an average downfield shift of only 12 Hz.[19] We interpret this to mean that the dibromo ketone has the structure shown as **19** and hence isomer C has structure **10**, leaving structure **11** for isomer D.



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The mixture, obtained from chlorination of **14**, was separated into its components by preparative glc and nmr data obtained (Table II). For this mixture

TABLE II

NMR DATA FOR THE BICYCLOOCTANONE ISOMERS FROM THE RING EXPANSION OF *exo*-2-ISOPROPENYLNORBORNAN-2-OL[a,e]

Isomer		ν_{CDCl_3}, Hz	$\nu_{C_6H_6}$, Hz	$\Delta^{CDCl_3}_{C_6H_6}$, Hz[b]
15	CH_3	76	62[d]	14
	CH_2Cl[c]	222 (J_{AB} = 11)	222 (J_{AB} = 11)	0
	$\Delta\nu_{AB}$	7	9	
16	CH_3	70	58	12
	CH_2Cl	207 (J_{AB} = 11)	196 (J_{AB} = 11)	11
	$\Delta\nu_{AB}$	31	37	
17	CH_3	72	56	16
	CH_2Cl	206 (J_{AB} = 11)	197 (J_{AB} = 11)	9
	$\Delta\nu_{AB}$	43	51	
18	CH_3	68	66	2
	CH_2Cl	216 (J_{AB} = 11)	197 (J_{AB} = 11)	19
	$\Delta\nu_{AB}$	11	9	

[a] Spectra were run on a 60-MHz instrument (Varian A-60A) with the compounds in 25% w/w solution. [b] See footnote *b*, Table I. [c] AB quartets are observed for all four of the bicyclooctanone isomers. See footnote *c*, Table I. [d] CH_3 (d), J = 0.7 Hz. [e] Chemical shift values are expressed in hertz downfield from TMS. J's are in hertz.

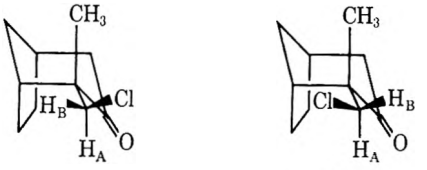
(17) F. Johnson, N. A. Starkovsky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965).

(18) J. Wolinsky, *J. Org. Chem.*, **26**, 704 (1961).

(19) The methylene of the chloromethyl appears as an AB quartet, so the problem is complicated, but a more detailed analysis has led us to the same conclusion.

of bicyclooctanones nmr integration of the α-carbonyl protons should serve to distinguish the 2-keto and 3-keto isomer pairs. This proved to be the case. The structures of the individual isomers of each pair were then assigned using the first two methods as previously employed for the cyclohexanones. Unlike the data for the cyclohexanones, the two methods arrived at the same assignments for the bicyclooctanone mixture.

The methyl doublet (J = 0.7 Hz) observed for isomer **15** was attributed to long-range coupling of the W type[20] with one of the chloromethyl protons. Although the coupling constant could not be measured, the coupling was observed to occur with H_A (the higher field proton; 218 Hz) as evidenced by broadening and fine splitting of the two lines for H_A. There are two conformers (**20** and **21**) of **15** which have the correct



20 **21**

geometry to give the observed long-range W type coupling. Assuming that the conformational preference will be the same in deuteriochloroform and benzene, the preferred conformer can then be assigned from the solvent shift data for H_A and H_B. Conformer **20** has H_A and H_B in different environments with respect to the solvent-shift plane (P) and H_A is predicted to undergo no shift while H_B is expected to undergo a fairly large upfield shift. Conformer **21**, on the other hand, has H_A and H_B both in the solvent-shift plane (P), and no solvent shift is expected for either. Since no solvent shift is observed for either

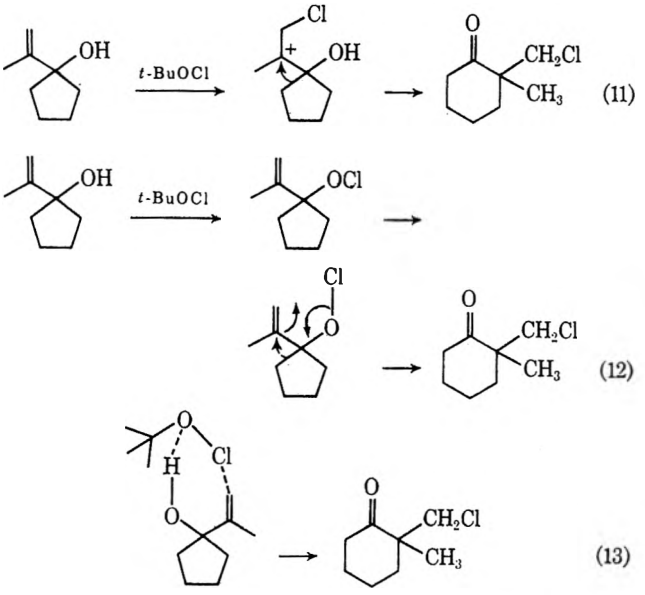
	ν_{CHCl_3}, Hz	$\nu_{C_6H_6}$, Hz	$\Delta^{CDCl_3}_{C_6H_6}$, Hz
H_A	218	218	0
H_B	226	226	0

H_A and H_B, conformer **21** is believed to be the preferred conformer.

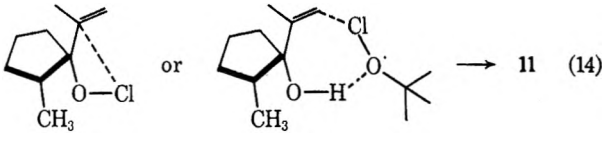
Stereochemistry and Mechanism.—In eq 7 and 10 it is shown that methine migration is preferred over methylene migration in these chlorinative ring-expansion reactions. Examination of the product distribution for the two reactions also shows that there is a definite configurational preference for the chloromethyl group in the product ketones. In the cyclopentanol **7** the isopropenyl group is trans to the methyl, and, if the norbornyl system is viewed as a substituted cyclopentane, then the isopropenyl group of the norbornanol **14** is trans to the ethano bridge. The configuration of the chloromethyl in the product ketones can then be consistently correlated with the geometry of both isopropenyl alcohols. The important factor is the trans–cis relationship of the chloromethyl group in the ketones to the alkyl group which corresponds to the 2-alkyl substituent in the alcohol. For the cyclohexanones this is the relationship of the chloromethyl to the 3- and 6-methyl substituents, and for the bicyclooctanones it is the relationship of the chloromethyl to the ethano bridge. The product distribution data for the two reactions can then be illustrated as follows, with the trans–cis ratio given for each isomer pair. No significance can be attached to the trans–cis ratio for the pair of 6-methylcyclohexanones, as isomerization may have occurred during the glc analysis. However, isomerization is not possible for the other three isomer pairs.

Isomer pair	Trans:cis ratio for the chloromethyl–alkyl group relationship
3-Methylcyclohexanones	14.4:1
2-Bicyclooctanones	2.3:1
3-Bicyclooctanones	1.8:1

Three mechanisms have been proposed for the chlorinative ring expansion with *tert*-butyl hypochlorite.[6] They are (1) electrophilic attack on the olefin by *tert*-butyl hypochlorite to generate an intermediate carbonium ion followed by an alkyl shift and collapse to product (intermolecular) (eq 11); (2) hypochlorite ester interchange followed by intramolecular reorganization (eq 12); and (3) a cyclic, concerted mechanism (eq 13).



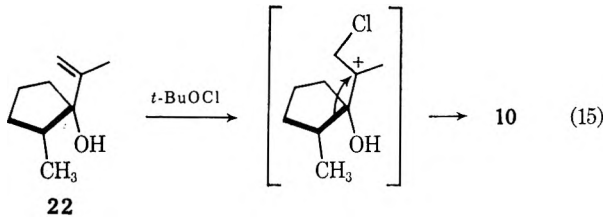
The observation that in these chlorinative ring-expansion reactions methine carbon migration is preferred over methylene is consistent with that expected of a ring-expansion reaction with some cationic character in the transition state (eq 11). Mechanisms 12 and 13 involve a concerted step, thus requiring that the isopropenyl group be in the conformation with the methyl over the face of the ring, thereby predicting **11** as the major product (eq 14), contrary to what is observed (eq 7).



The evidence thus points to a nonconcerted mechanism with some carbonium ion character in the transition state. Additionally, a preferred mechanism must account for the observed trans–cis ratio in the 3-methylcyclohexanone isomer pair. Inspection of

(20) Reference 14a, pp 334–341.

Dreiding models and Hirschfelder models indicates that the preferred conformation for *trans*-1-isopropenyl-2-methylcyclopentan-1-ol is the one with the methylene carbon situated over the face of the cyclopentane ring. If electrophilic attack by *tert*-butyl hypochlorite in this conformation (22) is then assumed, followed by a rapid alkyl shift to the intermediate "carbonium ion," the product predicted would be **10**, as is actually observed (eq 15). An additional requirement for



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obtaining the observed trans–cis ratio (14.4:1) is that the alkyl shift occurs before rotational equilibration of the carbonium ion can take place. The mechanism of eq 15 seems to best explain the observed product distribution from the chlorinative ring expansion of *trans*-1-isopropenyl-2-methylcyclopentan-1-ol. The mechanistic arguments applied to the 2-methylcyclopentanol system can be applied to *exo*-2-isopropenylnorbornan-2-ol as well.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 137 B spectrophotometer. The nmr spectra were taken on either a Varian A-60A or Varian T-60 spectrometer with tetramethylsilane (TMS) as the internal standard. The sweep width was 500 Hz, unless otherwise indicated. The glc work was performed with a Hewlett-Packard 5750 and Prepmaster, Jr.

All Grignard reactions were run under a dry nitrogen atmosphere. Grignard solvents (ether and tetrahydrofuran) were dried by distillation from sodium dispersion.

The melting points and boiling points are uncorrected. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

1-Isopropenylcyclopropanol (1).—To 2.68 g (0.11 mol) of magnesium turnings in 20 ml of tetrahydrofuran (THF) there was added dropwise over 45 min a solution of 10.65 ml (14.5 g, 0.12 mol) of 2-bromopropene in 80 ml of THF. The temperature was maintained at 40–50° throughout the addition, and stirring was continued for 30 min after the addition was complete. The solution of isopropenylmagnesium bromide was then cooled to −40° and a solution of 12.70 g (0.10 mol) of 1,3-dichloroacetone (Eastman) in 100 ml of THF was added over a 1-hr period with the temperature maintained at −40°. Stirring was continued for 30 min at −40° and for 3 hr longer, during which time the temperature was allowed to rise to 0°. There was then added simultaneously over a 1.5-hr period 400 ml of an ether solution containing 0.6 mol of ethylmagnesium bromide and a solution of 1.3 g (0.008 mol) of anhydrous ferric chloride in 100 ml of THF. The reaction mixture was allowed to stir for an additional 6 hr at 0°, followed by hydrolysis at 0° with a phosphate buffer solution (pH 7.0). The precipitated salts were filtered, and the filtrate was dried over anhydrous sodium sulfate. The solvent was removed under vacuum with a maximum pot temperature of 20° allowed. The residue was flash distilled with the pot temperature maintained under 20° to give 1.483 g (15%) of a clear, colorless liquid. The infrared spectrum of the product showed a strong hydroxyl band at 3300 cm^{-1} and absorptions at 3020, 1640, and 880 cm^{-1}. In addition, there was a medium band at 1770 cm^{-1}. The nmr spectrum of the product revealed the presence of two compounds in a 4:1 ratio. There was a complex multiplet of the AA'BB' type centered at δ 0.78 (cyclopropyl H), a quartet at 1.67 (isopropenyl $-CH_3$), a singlet at 3.88 (–OH), and two multiplets at 4.75 and 4.93 (vinyl H of isopropenyl group). These resonances were attributed to 1-isopropenylcyclopropanol. In addition, there was a singlet at δ 1.13 (*gem*-dimethyl), a triplet at 1.67 (β methylene H), and a triplet at 1.87 (α methylene H). These resonances were attributed to 2,2-dimethylcyclobutanone. Although the 1-isopropenylcyclopropanol was the major component initially, there was a slow conversion to 2,2-dimethylcyclobutanone which was complete after 24 hr as evidenced by the nmr spectrum. This rearrangement occurred either in carbon tetrachloride or neat. The 2,2-dimethylcyclobutanone was converted to its 2,4-dinitrophenylhydrazone (recrystallized from 95% ethanol), mp 139–140° (lit.[21] mp 140–141°).

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.08. Found: C, 51.64; H, 5.02.

1-Isopropenylcyclobutan-1-ol (3).—To 4.38 g (0.18 mol) of magnesium turnings in 30 ml of tetrahydrofuran (THF) there was added 16.9 g (0.09 mol) of 1,2-dibromoethane in 120 ml of THF. The addition was carried out over a 1.25-hr period with the temperature maintained at 50°. After the solution was stirred for an additional 30 min, 12.35 g (0.102 mol) of 2-bromopropene (Columbia Organics, 99+% purity) in 65 ml of THF was added to the reaction mixture over a 1.5-hr period. Stirring was continued for 45 min with the temperature maintained at 45° throughout the entire 2.25-hr period.

A solution of 4.2 g (0.06 mol) of cyclobutanone (Columbia Organics) in 40 ml of THF was added over a 1.25-hr period to the Grignard solution maintained at 50°. Stirring was continued for 15 hr at 50°. The reaction mixture was then cooled with an ice bath and hydrolyzed by the dropwise addition of saturated ammonium chloride solution. The THF solution was decanted from the precipitated salts and the precipitate was washed with three 100-ml portions of ether. The combined THF–ether solution was washed with two 100-ml portions of water and 100 ml of saturated sodium chloride solution. The combined water washings were extracted with 100 ml of ether; the THF–ether solution was washed once more with 100 ml of saturated sodium chloride solution and dried over anhydrous sodium sulfate. The ether and THF were removed by distillation at atmospheric pressure with the last traces removed by distillation at 60 mm (water pump). The viscous, yellow residue was flash distilled at 1 mm to give a clear, colorless liquid, which was distilled through a 4-cm column to yield 4.11 g (61%) of 1-isopropenylcyclobutan-1-ol: bp 48–50° (7.8 mm); $n^{25}D$ 1.4633; ir (film) 3350 (s, –OH), 3100 (w, $=CH_2$), 2950 (s, –CH), 1650 (m, $>C=CH_2$), 900 cm^{-1} (s, $>C=CH_2$); nmr (CCl_4) δ 1.77 (m, $-CH_3$), 2.10 (m, $-CH_2-$), 3.42 (s, –OH), 4.78 (m, trans vinyl H), 4.93 (m, cis vinyl H).

Anal. Calcd for $C_7H_{12}O$: C, 74.94; H, 10.80. Found: C, 74.83; H, 10.74.

Acid-Catalyzed Rearrangement of 1-Isopropenylcyclobutan-1-ol.—To 20 ml of 0.15 *M* 2,4-dinitrophenylhydrazine reagent was added 119.2 mg (1 mmol) of 1-isopropenylcyclobutan-1-ol. The solution was allowed to stand at room temperature for 3 days, during which period the 2,4-dinitrophenylhydrazone slowly crystallized as long, fine needles. The product was collected by filtration and dried to yield 149 mg (51%) of product, mp 142–143°. The 2,4-dinitrophenylhydrazone (recrystallized once from 95% ethanol) had mp 142–143° (lit.[22] mp 144°).

2-Methyl-2-(chloromethyl)cyclopentanone.—A solution of 1-isopropenylcyclobutan-1-ol (0.4475 g, 0.004 mmol) in 20 ml of alcohol-free chloroform was heated to 55° in a black-painted flask fitted with a reflux condenser. To the stirred solution was added 0.476 ml (0.434 g, 0.004 mol) of *tert*-butyl hypochlorite.[23] The reaction was completed in 2 hr as evidenced by a negative test for *tert*-butyl hypochlorite with potassium iodide–starch test paper. The chloroform solution was passed through a short column of alumina, and the chloroform was removed by distillation at atmospheric pressure. The pale-yellow liquid residue was distilled twice with a short-path apparatus to yield 0.4281g (73%) of 2-methyl-2-(chloromethyl)cyclopentanone: bp 46–48° (1.8 mm); $n^{25}D$ 1.4663; ir (film) 2950 (m, –CH), 1740 (s, C=O), 740 (m, –CCl); nmr (CCl_4) δ 1.05 (s, $-CH_3$), 2.08 (broad m, $-CH_2-$), 3.46 (AB quartet, J = 11 Hz, $-CH_2Cl$).

Anal. Calcd for $C_7H_{11}OCl$: C, 57.33; H, 7.56. Found: C, 57.21; H, 7.46.

Reaction of 1-Isopropenyl-1-indanol (4) with *tert*-Butyl Hypochlorite.—To a magnetically stirred solution of 0.3485 g (2

(21) H. Bestian and D. Guenther, *Angew. Chem.*, **75**, 841 (1963).
(22) C. F. Wilcox, Jr., and M. Mesirov, *J. Org. Chem.*, **25**, 1841 (1960).
(23) D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Englewood Cliffs, N. J., 1969, p 363.

mmol) of 1-isopropenyl-1-indanol[24] in 10 ml of alcohol-free chloroform in a black-painted flask at 55° was added 0.24 ml (0.217 g, 2 mmol) of freshly prepared *tert*-butyl hypochlorite.[23] After complete reaction (38.5 hr, negative potassium iodide–starch test) the solvent was removed *in vacuo*. The viscous, yellow residue (0.411 g) was subjected to infrared and glc analysis. The infrared spectrum of this material contained carbonyl bands at 1720 and 1680 cm^{-1}, with the more intense band at 1720 cm^{-1}. Glc analysis was carried out with a 8 ft × 0.25 in., 20% diethylene glycol succinate on Chromosorb W, 60–80 mesh column at a column temperature of 172° and a helium flow of 150 ml/min. The chromatogram revealed three peaks with retention times of 19 (minor), 33 (major), and 39.5 min (major). The minor peak at 19 min was not identified, and planimetric integration showed it to be 11% of the total mixture. Based on glc analysis, the yield of tetralones was 0.266 g (88%). Planimetric integration of the two major peaks at 33 (isomer **5**) and 39.5 min (isomer **6**) gave a ratio of 41:59. Collection of the two peaks by glc and their infrared spectra and elemental analyses gave the following data. Isomer **5** had ir (CCl_4) 1680 cm^{-1}. *Anal.* Calcd for $C_{12}H_{13}OCl$: C, 69.06; H, 6.29. Found C, 68.78; H, 6.15. Isomer **6** had ir (CCl_4) 1720 cm^{-1}. *Anal.* Calcd for $C_{12}H_{13}OCl$: C, 69.06; H, 6.29. Found: C, 68.93; H, 6.21.

trans-**1-Isopropenyl-2-methylcyclopentan-1-ol** (**7**).—to 7.3 g (0.30 mol) of magnesium turnings (Fisher, Laboratory Reagent) in tetrahydrofuran (THF) was added, dropwise with stirring, 13.0 ml (28.2 g, 0.15 mol) of 1,2-dibromoethane in 200 ml of THF over a period of 2 hr while the temperature was maintained at 50°. After stirring for an additional 30 min at 50°, 15.1 ml (20.6 g, 0.17 mol) of 2-bromopropene (Columbia Organics, 99+% purity) in 110 ml of THF was added over a period of 1.5 hr with the temperature maintained at 45°. The stirring was continued at 45° for 30 min after the addition was completed.

A solution of 9.814 g (0.10 mol) of 2-methylcyclopentanone[25] in 70 ml of THF was added to the Grignard solution at 50° over a 2.5-hr period. Stirring was continued for 14 hr with the reaction temperature maintained at 50° throughout. The reaction mixture was cooled with an ice bath, hydrolyzed, and worked up as described for the preparation of 1-isopropenyl cyclobutan-1-ol. The product was fractionally distilled through a 20-cm Podbielniak column to yield 3.90 g (28%) of pure *trans*-1-isopropenyl-2-methylcyclopentan-1-ol: bp 62° (9.2 mm); $n^{25}D$ 1.4692; ir (neat) 3400 (m, -OH), 2825 (m), 1650 (m, $=CH_2$), 950 (m), 900 cm^{-1} (m); nmr (CCl_4) δ 0.83 (d, J = 6 Hz, $-CH_3$), 1.70 (m, $-CCH_3$), 1.70 (m, $-CH_2-$), 4.82 (m, trans vinyl H), 5.02 (m, cis vinyl H).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.84; H, 11.35.

Reaction of *trans*-1-Isopropenyl-2-methylcyclopentan-1-ol with *tert*-Butyl Hypochlorite.—To a magnetically stirred solution of 1.05 g (7.5 mmol) of *trans*-1-isopropenyl-2-methylcyclopentan-1-ol in 40 ml of alcohol-free chloroform in a black-painted flask at 55° was added 0.92 ml (0.84 g, 7.7 mmol) of freshly prepared *tert*-butyl hypochlorite.[23] After completion of the reaction (8 hr, negative potassium iodide–starch test) the solvent was removed *in vacuo* to leave 1.29 g of a clear, yellow oil. The infrared spectrum of this material had a strong carbonyl band at 1720 cm^{-1}. Glc analysis was performed with a 16 ft × 0.25 in., 20% diethylene glycol succinate on Chromosorb W, 60–80 mesh column, with a column temperature of 180° and a helium flow of 46 ml/min. The chromatogram revealed at least 15 minor peaks with retention times in the range 0–13 min, and four major peaks with retention times of 16 (isomer A), 20 (isomer B), 25 (isomer C), and 29.5 min (isomer D). Planimetric integration gave the following percentages for the total of the four major peaks: isomer A, 15%; isomer B, 8%; isomer C, 72%; and isomer D, 5%. No attempt was made to identify any of the minor peaks in the 0–13 min range. The four major peaks were collected with a 20 ft × 0.375 in., 20% diethylene glycol succinate on Chromosorb W, 60–80 mesh column. Temperature programming was employed with a postinjection interval of 20 min at 145°, a programmed increase of 2°/min to 188°, and an additional 20 min at the upper limit of 188°. The helium flow rate was 150 ml/min, and the total time of the cycle was 54 min. Nmr data in deuteriochloroform and benzene were collected for all four isomers (Table I). An elemental analysis was obtained for isomer C.

Anal. Calcd for $C_9H_{15}OCl$: C, 61.88; H, 8.67. Found: C, 61.72; H, 8.73.

exo-**2-Isopropenyl-2-norbornanol** (**14**).—The procedure was identical with that used for the preparation of *trans*-1-isopropenyl-2-methylcyclopentan-1-ol. A 19.83-g (0.18 mol) portion of 2-norbornanone was allowed to react, with all other reagents scaled up accordingly. After the usual work-up, distillation through a Vigreux column yielded 22.58 g (82%) of *exo*-2-isopropenyl-2-norbornanol: bp 49–51° (0.8 mm); ir (film) 3600, 3450, 1650, 900 cm^{-1}; nmr (CCl_4) δ 1.80 (m, $-CCH_3$), 4.78 (m, trans vinyl H), 4.92 (m, cis vinyl H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 78.92; H, 10.61.

Reaction of *exo*-2-Isopropenyl-2-norbornanol with *tert*-Butyl Hypochlorite.—To a magnetically stirred solution of 3.81 g (25 mmol) of *exo*-2-isopropenyl-2-norbornanol in 125 ml of alcohol-free chloroform was added 3.10 ml (2.82 g, 26 mmol) of freshly prepared *tert*-butyl hypochlorite.[23] After completion of the reaction (8 hr, negative potassium iodide–starch test), the solvent was removed *in vacuo* to leave 4.46 g of a clear, yellow oil. The infrared spectrum of this material had a strong carbonyl band at 1700 cm^{-1}. Glc analysis was carried out with a 16 ft × 0.25 in., 10% ethylene glycol succinate on Chromosorb W, 60–80 mesh column with a column temperature of 150° and a helium flow rate of 60 ml/min. The chromatogram showed two very minor peaks at 18–20 min and four major peaks at 27 (isomer **15**), 30 (isomer **16**), 34 (isomer **17**), and 38 min (isomer **18**). Planimetric integration gave the following percentages for the four major peaks: isomer **15**, 23%; isomer **16**, 11%; isomer **17**, 25%; and isomer **18**, 41%. The four major peaks were collected by preparative glc using a 6 ft × 0.75 in., 20% diethylene glycol succinate on Chromosorb W, 10–60 mesh column, with a 150° column temperature and a nitrogen flow rate of 300 ml/min. Four fractions were collected corresponding to each of the four peaks. The first and the fourth fractions contained over 75% of the desired isomer and were further purified by a second pass through the 6 ft × 0.75 in. column. The second and third fractions were about 50:50 mixtures of the desired isomers and they were further purified by collecting from a 25 ft × 0.375 in., 15% ethylene glycol succinate on Chromosorb W, 60–80 mesh column, at 170° column temperature and a nitrogen flow rate of 100 ml/min. Nmr data in deuteriochloroform and benzene were obtained for the four isomers (Table II). An elemental analysis was obtained for isomer **18**.

Anal. Calcd for $C_{10}H_{15}OCl$: C, 64.33; H, 8.11. Found: C, 64.18; H, 8.09.

Registry No.—**1**, 40791-85-3; **2**, 1192-14-9; **2** DNP, 4070-16-0; **3**, 40791-88-6; **4**, 19063-65-1; **5**, 40791-90-0; **6**, 40791-91-1; **7**, 40791-92-2; **8**, 40791-93-3; **9**, 40791-94-4; **10**, 40791-95-5; **11**, 40791-96-6; **14**, 40791-97-7; **15**, 40791-98-8; **16**, 40791-99-9; **17**, 40792-00-5; **18**, 40792-01-6; *tert*-butyl hypochlorite, 507-40-4; 2-bromopropene, 557-93-7; 1,2-dibromoethane, 106-93-4; cyclobutanone, 1191-95-3; 2,2-dimethylcyclopentanone, 4541-32-6; 2-methyl-2-(chloromethyl)cyclopentanone, 40792-02-7; 2-methylcyclopentanone, 1120-72-5; 2-norbornanone, 497-38-1.

(24) C. J. Cheer and C. R. Johnson, *J. Amer. Chem. Soc.*, **90**, 178 (1968).

(25) The 2-methylcyclopentanone was prepared from 1-methylcyclopentene by the hydroboration–dichromate oxidation procedure of H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2544 (1961).

Liquid Crystals. IV. Effects of Terminal Substituents on the Nematic Mesomorphism of *p*-Phenylene Dibenzoates[1]

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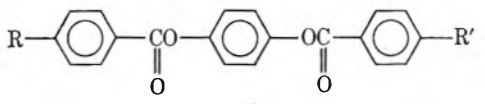
New *p*-phenylene dibenzoates with various end groups were prepared and their phase transition temperatures determined. The data for these compounds and for other terminally substituted *p*-phenylene dibenzoates described in the literature were then examined for trends in nematic liquid crystalline behavior. Only 7 of the 63 esters do not exhibit a nematic mesophase. The marked tendency of this molecular system to be nematic is further shown by the mesomorphism of three esters having only one terminal substituent. Of the end groups for which data are available, long-chain alkoxy groups are most effective at lowering the melting point; CN, NO_2, COOMe, and Br are most effective at raising it. The highest nematic–isotropic transition temperatures are produced by CN, COOMe, MeO, and COOEt, and the lowest by COO-*n*-Bu, *i*-Pr, cyclohexoxy, and *i*-BuO. Unsymmetrical di-*n*-alkoxy esters are the lowest melting *p*-phenylene dibenzoates and have the broadest nematic temperature ranges. An attempt is made to rationalize the data, and analogies with other nematic molecular systems are discussed. In the course of the investigation, new para-substituted benzoic acids and *p*-hydroxyphenyl benzoates were also synthesized.

Attempts to correlate the properties of compounds with their molecular structures are common in chemical research. A familiar example is the systematic variation of substituent groups on a physiologically active parent compound to determine the effect of these changes on activity. Mesomorphic (liquid crystalline)[2-4] molecular systems have been investigated in a similar manner to ascertain the effects of structural variations on the temperature range over which the mesophase is stable. Sometimes, the objective is to "tailor" the range to fit a particular application. Usually, there is also the broader goal of finding correlations between specific structural modifications and changes in liquid crystallinity that might be applicable in some degree to other mesomorphic systems. Ideally, if the latter goal is considered, the original compound's mesophase should exist over a broad temperature range. Otherwise, even minor alterations in structure may destroy mesomorphism altogether. If most structural changes accomplish this destruction, their deleterious effect is established, but the relative extent to which they are disruptive remains unknown.

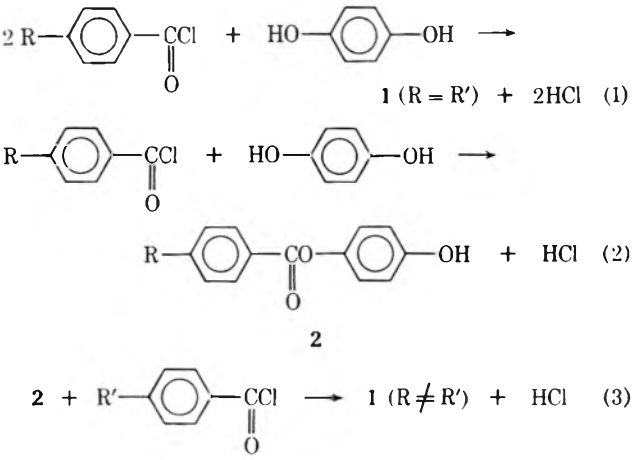
p-Phenylene di-*n*-alkoxybenzoates (**1**, R = R′ = *n*-alkoxy) have been shown[5-7] to exhibit nematic



1

mesophases[2-4] with broad ranges terminating at high temperatures. Introduction of a methyl substituent on the central phenylene ring,[7] two very different terminal alkoxy groups (*e.g.*, CH_3O and n-$C_8H_{17}O$),[8] or replacement of the alkoxy end groups by Cl, NO_2, or CO_2Et[6a] do not destroy mesomorphism. These results suggested that the nematic mesophase of system **1** might survive still more drastic structural variations and, therefore, that the system would be excellent for an extensive study of the effects of structural changes on nematic behavior. This paper describes an investigation of major variations of R and R′.

Ten symmetrical and 11 unsymmetrical esters of type **1** were prepared by the processes shown in eq 1–3. During the investigation, three new para-substituted benzoic acids and three new phenols of type **2** were also prepared. The phase transition temperatures of these products were determined using a hot stage polarizing microscope.



2

Experimental Section

Para-Substituted Benzoic Acids.—The methyl, isopropyl, *tert*-butyl, bromo, chloro, and cyano acids are commercial products. The isobutoxy, cyclohexoxy, and 2-ethoxyethoxy acids were prepared by reaction of ethyl *p*-hydroxybenzoate with the appropriate alkyl bromide and saponification of the resulting ethyl *p*-alkoxybenzoate in ethanolic KOH solution.[5] Recrystallization solvent, yield (based on ethyl *p*-hydroxybenzoate), and melting point data are as follows: *i*-C_4H_9O acid, benzene, 86%, 142°; cyclohexoxy acid, EtOH, 12%, 185°; $EtOCH_2CH_2O$ acid, benzene, 90%, 134°. Apparently, Steinsträsser[9] has prepared the last-named compound, but does not describe its properties.

Benzoyl Chlorides.—Benzoyl and *p*-nitrobenzoyl chloride were purchased. The others were obtained from the corresponding

(1) (a) This work was supported by a grant from the Research Council of the University of North Carolina at Greensboro and a summer stipend from the university. (b) Previous paper in this series: M. A. Andrews, D. C. Schroeder, and J. P. Schroeder, *J. Chromatogr.*, **71**, 233(1972).

(2) G. H. Brown and W. G. Shaw, *Chem. Rev.*, **57**, 1049 (1957).

(3) G. W. Gray, "Molecular Structure and the Properties of Liquid Crystals," Academic Press, New York, N. Y., 1962.

(4) A. Saupe, *Angew. Chem., Int. Ed. Engl.*, **7**,97 (1968).

(5) M. J. S. Dewar and J. P. Schroeder, *J. Org. Chem.*, **30**, 2296 (1965).

(6) (a) M. J. S. Dewar and R. S. Goldberg, *J. Org.Chem.*, **35**, 2711 (1970); (b) *J. Amer. Chem. Soc.*, **92**, 1582 (1970).

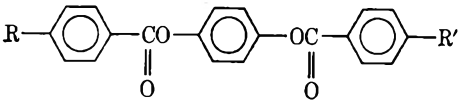
(7) S. L. Arora, J. L. Fergason, and T. R. Taylor, *J. Org. Chem.*, **35**, 4055 (1970).

(8) S. A. Haut, D. C. Schroeder, and J. P. Schroeder, *J. Org. Chem.*, **37**, 1425 (1972).

(9) R. Steinstrasser, *Angew. Chem., Int. Ed. Engl.*, **11**, 633 (1972).

TABLE I

p-PHENYLENE DIBENZOATES[a]



Registry no.	R	R′	Synthetic method	Recrystn solvent	Yield, %	Transition temp, °C Mp	Transition temp, °C N–I[b]
14210-97-0	H	H	A	EtOH	60	207[c]	*d*
40781-77-9	H	Me	A	EtOH	81	172	*d*
40781-78-0	H	MeO	A	EtOH	76	157	173
40781-79-1	H	*i*-BuO	A	EtOH	90	153.5	*d*
40781-80-4	H	*n*-$C_6H_{13}O$	A	EtOH	89	119	150
40864-79-7	H	$EtOCH_2CH_2O$	A	EtOH	92	134	(117)[e]
40781-81-5	Me	Me	A	Dioxane	63	231.5	236
40781-82-6	*i*-Pr	*i*-Pr	C	EtOH	8	161.5	*d*
40781-83-7	*t*-Bu	*t*-Bu	B	EtOAc	58	204	*d*
40781-84-8	MeO	Me	A	1. EtOH–dioxane 2. EtOH	73	199	265
40781-85-9	MeO	Cl	A	EtOH	93	196	275
40781-86-0	MeO	Br	A	EtOH–dioxane	81	214	277
40781-87-1	MeO	*i*-BuO	A	EtOH	73	155.5	236.5[f]
40781-88-2	MeO	Cyclohexoxy	B	EtOH	89	174	299
40781-89-3	MeO	$EtOCH_2CH_2O$	A	EtOH	60	127[g]	237
40781-90-6	*i*-BuO	*i*-BuO	A	EtOH	75	174	181
40781-91-7	Cyclohexoxy	Cyclohexoxy	B	EtOH	59	203	(163)[e]
40781-92-8	$EtOCH_2CH_2O$	$EtOCH_2CH_2O$	A	EtOH	76	125	188.5
40781-93-9	Br	Br	A	Dioxane	73	255	(252)[e]
40781-94-0	CN	CN	B	Dioxane	74	331.5	353.5
24706-98-7	NO_2	NO_2	B	Dioxane	55	262[h]	281[h]

[a] Satisfactory analytical data (±0.4% for C and H) were reported for all new compounds listed in the table. [b] Nematic–isotropic. [c] Lit. mp 204°: M. T. Bogert and H. P. Howells, *J. Amer. Chem. Soc.*, 52, 837 (1930). [d] Not liquid crystalline. [e] Monotropic transition observed only on cooling. [f] This compound also exhibited a monotropic transition (see footnote *e*) from nematic to smectic at 125.5°. [g] Another crystalline modification melting at 109.5° to nematic liquid was also observed. [h] Mp 260° and N–I transition temperature 266° have been reported for this compound (ref 6a).

acid by treatment with thionyl chloride at reflux in the presence of pyridine as catalyst. Excess thionyl chloride was distilled to give the acid chloride as a residue product. *p*-Ethoxyethoxybenzoyl chloride crystallized on cooling as needles, mp 43–45°.

***p*-Hydroxyphenyl Benzoate (2) Starting Materials.**—The *p*-methoxy- and *p*-*n*-hexoxybenzoates had been synthesized earlier by S. A. Haut.[8] *p*-Hydroxyphenyl benzoate, mp 167° (lit.[10] mp 164°), was prepared from benzoyl chloride and hydroquinone by essentially the same procedure.

***p*-Phenylene Dibenzoates (1). Method A.**—Most of the esters were prepared by the procedure that had proven to be satisfactory earlier.[5,8] Typically, for symmetrical esters, a solution of 0.0060 mol of hydroquinone in 30 ml of dry pyridine was added with swirling to a solution of 0.018 mol of acid chloride in 30 ml of dry pyridine. After standing for 24–48 hr, the mixture was added to 300 ml of 3 *N* hydrochloric acid. The resulting precipitate was filtered, washed with water, and stirred with 200 ml of 5% aqueous Na_2CO_3 solution for 1 hr. The crude product was recovered by filtration, washed with water and then ethanol, and recrystallized from a suitable solvent. The procedure for unsymmetrical esters was similar except that the reaction was initiated by addition of a solution of the hydroxyphenyl benzoate to a solution of the acid chloride (molar ratio 1:3), both in anhydrous pyridine.

This method was unsuccessful when applied to the preparation of the di-*p*-isopropyl and di-*p*-*tert*-butyl benzoates. The only esters isolated were small amounts of *p*-hydroxyphenyl *p*-alkyl benzoates (see below). Accordingly, the following procedural modifications were tried.

Method B.—The only change here was to add the reaction mixture to water instead of hydrochloric acid to precipitate the product. The di-*tert*-butyl benzoate was obtained in this manner. The method was subsequently used to prepare several other esters (see Table I). In the synthesis of *p*-phenylene di-*p*-cyclohexoxybenzoate, the monoester (see below) was a major by-product.

Method C.—The di-*i*-propylbenzoate was prepared using classic Schotten–Baumann conditions. *p*-Isopropylbenzoyl chloride (0.0040 mol) was added with stirring to a solution of 0.0010 mol of hydroquinone and 2.0 g of NaOH in 8 ml of water. After 1.5 hr, the product was recovered by filtration, washed with water, and recrystallized.

In all three methods, excess acyl chloride can be recovered (as the acid) by treatment of the alkaline filtrate and/or wash liquor with excess hydrochloric acid. The results for the dibenzoates are summarized in Table I.

***p*-Hydroxyphenyl Benzoate (2) Products.**—**2**, R = *i*-C_3H_7, mp 127°, and **2**, R = *t*-C_4H_9, mp 156°, were the sole products of attempts to prepare the corresponding dibenzoates by method A. The yields were 2 and 4%, respectively. **2**, R = cyclohexoxy, mp 133°, was a major by-product (33% yield) in the synthesis of the corresponding dibenzoate by method B. All three compounds were recrystallized from aqueous ethanol.

Transition Temperatures.—These were determined with a Reichert "Thermopan" polarizing microscope equipped with a Kofler micro hot stage. The instrument was calibrated against pure compounds of known melting points.

Analyses.—The elemental microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland, and by Galbraith Laboratories, Inc., Knoxville, Tenn. Satisfactory analytical data (±0.4% for C and H) were reported for the new *p*-alkoxybenzoic acids and *p*-hydroxyphenyl benzoates.

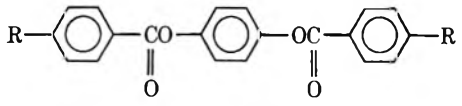
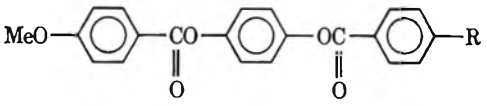
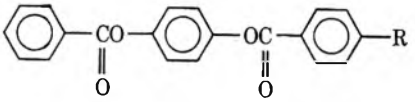
Results and Discussion

The esters in Table I fall into three general categories of end group combinations: R–R, MeO–R, and H–R. In Table II, system 1 esters from this work and from the literature are arranged, within each of the three end-group categories, in order of increasing N–I transition temperature. Of the 42 esters in Table II, representing a wide variation in end groups,

(10) F. Kehrmann, M. Sandoz, and R. Monnier, *Helv. Chim. Acta*, 4, 941 (1921).

TABLE II

EFFECTS OF TERMINAL SUBSTITUENTS ON NEMATIC-ISOTROPIC TRANSITION TEMPERATURES AND MELTING POINTS OF *p*-PHENYLENE DIBENZOATES[a]

Registry no.	R	N–I temp, °C	Mp, °C
	Symmetrical Esters		
			
	H		207
	i-Pr		161.5
	t-Bu		204
1819-04-1	COO-*n*-Bu	155[b]	139[b]
	Cyclohexoxy	163	203
	i-BuO	181	174
	$EtOCH_2CH_2O$	188.5	125
24706-96-5	*n*-$C_8H_{17}O$	195[c]	122[c]
1819-00-7	*n*-$C_7H_{15}O$	199[c]	122[c]
24706-99-8	F	199[d]	210[e]
1818-99-1	*n*-$C_6H_{13}O$	213[c]	124[c]
1819-03-0	COO-*n*-Pr	219[b]	193[b]
33903-92-3	*n*-$C_5H_{11}O$	222[f]	145[f]
	Me	236	231.5
1818-98-0	*n*-BuO	241[g]	153[g]
5411-00-7	Cl	246[e]	226[e]
24704-16-3	*n*-PrO	249[g]	175[g]
	Br	252	255
	NO_2	281	262
24706-93-2	EtO	287[g]	226[g]
1819-02-9	COOEt	298[b]	203[b,e]
1962-76-1	MeO	300[b]	222[b]
1819-01-8	COOMe	343 dec[b]	262[b]
	CN	353.5	331.5
	MeO-Terminated Esters		
			
	H	173	157
	Cyclohexoxy	229	174
33905-73-6	*n*-$C_8H_{17}O$	229[f]	125[f]
33905-72-5	*n*-$C_7H_{15}O$	234[f]	127[f]
	i-BuO	236.5	155.5
40781-89-3	$EtOCH_2CH_2O$	237	127 (109.5)
33905-71-4	*n*-$C_6H_{13}O$	244[f]	125[f]
33905-70-3	*n*-$C_5H_{11}O$	253[f]	137[f]
	Me	265	199
33905-69-0	*n*-BuO	266[f]	134[f]
40781-85-9	Cl	275	196
33905-68-9	*n*-PrO	277[f]	167[f]
	Br	277	214
33905-67-8	EtO	295[f]	213[f]
	MeO	300[b]	222[b]
	H-Terminated Esters		
			
	H		207
	Me		172
	i-BuO		153.5
	$EtOCH_2CH_2O$	117	134
	n-$C_6H_{13}O$	150	119
	MeO	173	157

[a] Data from sources other than Table I are indicated by footnotes. [b] Reference 5. [c] Reference 7. [d] Compound is not nematic. Value estimated by extrapolation of N–I transition curve in binary phase diagram for this ester and the dimethoxy ester (ref 6a). [e] Reference 6a. [f] Reference 8. [g] Reference 6.

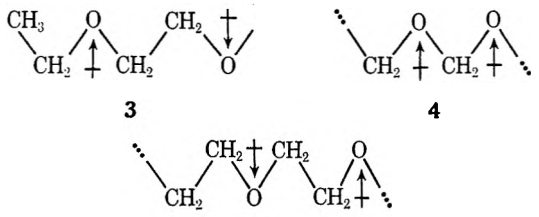
only seven do not exhibit a nematic mesophase.[11] The marked tendency of the system to be mesomorphic is particularly well shown by the three nematic compounds having only one terminal substituent. When the data in Table II are examined, trends are apparent that may be summarized as follows. Bulky, relatively nonpolar, long-chain alkoxy groups give the lowest melting points, while more compact, polar groups (CN, NO_2, COOMe, halogen, EtO MeO, Me) give the highest. The $EtOCH_2CH_2O$ substituent is about as effective as the long-chain alkoxy groups in lowering the melting point. The "abnormally" high values for MeO and H in the MeO–R and H–R series, respectively, reflect the importance of symmetry to crystalline lattice stability.

End group bulk and polarity seem to be the principal factors that influence the N–I transition temperature also. The highest values are provided by relatively compact, polar substituents (CN, COOMe, MeO). Bulky and, particularly, branched groups with little polarity give low N–I points. The effect of branching is shown by the results for isomeric alkyl moieties (cyclohexoxy < *n*-$C_6H_{13}O$, *i*-BuO < *n*-BuO). The combined effects of increasing bulk and decreasing polarity are demonstrated by the homologous series *n*-RO (Me > Et > Pr > Bu > C_5H_{11} > C_6H_{13} > C_8H_{17}) and COO-*n*-R (Me > Et > Pr > Bu). However, there appears to be a group size below which an adverse effect on mesomorphism sets in, probably because the molecule becomes too short. Thus, H and the highly polar F are well below Me and Cl in the N–I temperature order. The fact that Cl and Br give very similar values, despite the larger size and lower electronegativity of the latter, may be associated with the greater polarizability of Br.

The results are in accord with generally accepted theories of molecular structural influences on melting and N–I transition points. The melting temperature is enhanced by symmetry and strong intermolecular attractive forces. The latter are provided by polar and easily polarizable segments of the molecule. Bulky, nonpolar groups, because they inhibit close approach of neighboring molecules while contributing little or nothing to intermolecular attraction, have a lowering effect on the melting point. The same factors apply also to nematic mesophase stability except that they are conditioned by the requirement that a nematic compound must have rod-shaped molecules; *i.e.*, bulk along the longitudinal molecular axis is not nearly so deleterious as the same bulk located laterally so that it broadens the molecule. Our data for $EtOCH_2CH_2O$ appeared, at first, to be anomalous. The group is about the same size as *n*-$C_5H_{11}O$ and, presumably, more polar because of the additional ether oxygen. However, in Table II, the melting point order is *n*-$C_5H_{11}O$ > $EtOCH_2CH_2O$ and the N–I point order *n*-$C_5H_{11}O$ > *n*-$C_6H_{13}O$ > $EtOCH_2CH_2O$. For the symmetrical esters, the N–I temperature of $EtOCH_2CH_2O$ even falls below those of *n*-$C_7H_{15}O$ and *n*-$C_8H_{17}O$. This suggests that the opposing dipoles in the extended $EtOCH_2CH_2O$ group (**3**) render it less polar than a *n*-alkoxy group of similar length with its unopposed C–O–C dipole. The situation recalls the insolubility

(11) In addition, 21 nematic unsymmetrical di-*n*-alkoxy esters, which are not included in Table II, have been prepared.[8]

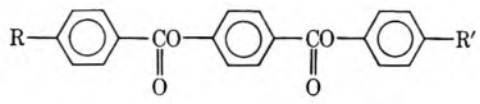
of poly(formaldehyde) (**4**) in water, which appears to be anomalous in that poly(ethylene oxide) (**5**) is readily soluble. Superficially, **4** should be more soluble



3 **4**

5

since it has the higher oxygen content. However, the C–O–C dipoles in **4** are all in the same direction, resulting in powerful intermolecular attractive forces, whereas these forces are weaker in **5** because of its alternating opposed dipoles. Individual molecules of **5** are more readily hydrated and pulled into aqueous solution from the surfaces of polymer particles. Steinsträsser's results[9] for the $EtOCH_2CH_2O$ end group in terminally substituted phenyl *p*-benzoyloxybenzoates (**6**) agree with ours in the **1** system. For **6**, R′ = *n*-Bu,

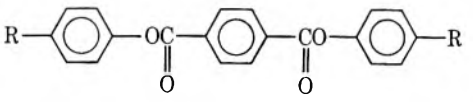


6

R = alkoxy, he found that the nematic ranges are R = *n*-$C_{10}H_{21}O$, 91–172°; R = $EtOCH_2CH_2O$, 99–170°; R = MeO, 107–235°; R = *n*-BuO, 113–212°; *i.e.*, the $EtOCH_2CH_2O$ ester melts well below the *n*-BuO ester (only 8° above the *n*-$C_{10}H_{21}O$ ester), and its N–I temperature is the lowest of the four. Working with Schiff bases, Dietrich and Steiger[12] have also observed nematic mesophase destabilization on replacement of $-CH_2-$ by $-O-$ in *n*-alkoxy substituents, and have drawn similar conclusions relating the effect to intermolecular forces.

Of the terminal substituents in Table II, long-chain alkoxy groups are most effective in lowering the melting point, while CN, NO_2, COOMe, and Br are most effective in raising it. The highest N–I temperatures are produced by CN, COOMe, MeO, and COOEt, the lowest by COOBu, cyclohexoxy, and *i*-BuO. Unsymmetrical di-*n*-alkoxy esters[8] are the lowest melting ($C_6H_{13}O$–OC_8H_{17}, mp 106°; $C_5H_{11}O$–OC_7H_{15}, mp 108°) and have the broadest nematic ranges (MeO–OBu, 134–266°; EtO–OBu, 150–270°) of the type **1** compounds that have been described to date. However, we are certain that terminal *n*-alkyl groups[9,12–20] and methyl[7,18,19] or chloro[20] substituents on the phenylene rings would provide still lower melting points without destroying nematic mesomorphism in consideration of data reported for other molecular systems.

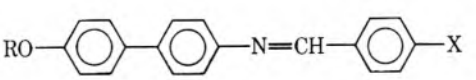
It is pertinent to compare the effects of end group variation on nematic behavior in type **1** esters with those in the closely related diphenyl terephthalates (**7**) and phenyl *p*-benzoyloxybenzoates (**6**). Dewar



7

and Goldberg[6a] compared the N–I transition temperatures of five **1**–**7** ester pairs with identical end groups and found the value for the **1** ester to be invariably higher. Their explanation is that an electron-releasing end group increases the polarity of the C=O group in **1** and hence stabilizes the mesophase; there is little effect on **7**. On the other hand, an electron-withdrawing end group has little effect on **1**, but destabilizes the mesophase in **7** by reducing the polarity of the C=O group. Extension of the comparison to include five *n*-alkoxy end groups lends further support to this argument. The N–I temperature difference between **1** and **7** esters is 11–12° for *n*-$C_7H_{15}O$, *n*-$C_6H_{13}O$, *n*-BuO, and *n*-PrO (electron releasing), 20–23° for MeO, EtO, and Cl (electron releasing but also electron withdrawing inductively), 25° for F (strongly electron withdrawing), and 54–63° for NO_2 and COOEt (powerfully electron withdrawing in **7** since the N=O and C=O bonds are conjugated with the para oxygen, producing inordinately low N–I temperatures). Four of the type **6** esters described by Steinsträsser[9] have the same end groups (*n*-alkoxy) as known esters of type **1**.[8] In each of these four directly comparable pairs, the N–I transition temperature of the **1** ester is higher than that of the **6** ester. Again, this is consistent with enhancement of nematic mesophase stability by an electron-releasing end group that is in conjugation with a C=O group as suggested by Dewar and Goldberg.[6a] Both alkoxy substituents in **1** are so situated, whereas only one is in **6**. In both systems, the N–I temperature decreases with increasing end group length. The difference between N–I values for each ester pair also decreases in this order, suggesting that, as the end groups become longer, this effect becomes dominant over polarity variations in the centers of the molecules.

Correlations can also be demonstrated for type **1** esters *vs.* dissimilar systems. Dave and Dewar[21] determined the effects on nematic properties of adding nonmesomorphic para-substituted Schiff bases to *p*-azoxyanisole. From these data, they arranged the end groups of the Schiff bases in order of decreasing efficiency in promoting nematic mesomorphism. Gray[22] compared this order with the effects of various terminal groups (X) on the N–I transition temperatures of two homologous Schiff base systems (**8a** and **8b**).



8a, R = Me
b, R = *n*-$C_8H_{17}O$

(12) H. J. Dietrich and E. L. Steiger, *Mol. Cryst. Liq. Cryst.*, **16**, 263 (1972).
(13) (a) H. Kelker and B. Scheurle, *Angew. Chem., Int. Ed. Engl.*, **8**, 884 (1969); (b) H. Kelker, B. Scheurle, R. Hatz, and W. Bartsch, *ibid.*, **9**, 962 (1970).
(14) R. Steinsträsser and L. Pohl, *Tetrahedron Lett.*, 1921 (1971).
(15) D. L. Fishel and Y. Y. Hsu, *Chem. Commun.*, 1557 (1971).
(16) J. Malthete, M. Leclercq, J. Gabard, J. Billard, and J. Jacques, *C. R. Acad. Sci., Paris, Ser. C*, **273**, 265 (1971).
(17) W. R. Young, A. Aviram, and R. J. Cox, *Angew. Chem., Int. Ed. Engl.*, **10**, 410 (1971); *J. Amer. Chem. Soc.*, **94**, 3976 (1972).
(18) W. R. Young, I. Haller, and D. C. Green, *J. Org. Chem.*, **37**, 3707 (1972).
(19) W. R. Young and D. C. Green, private communication.
(20) J. P. van Meter and B. H. Klanderman, Abstracts, 4th International Liquid Crystal Conference, Kent, Ohio, Aug 1972, No. 161.
(21) J. S. Dave and M. J. S. Dewar, *J. Chem. Soc.*, 4305 (1955).
(22) Reference 3, p 132.

When the groups common to these three system, type 7 esters, and the esters in Table II are examined together (Table III), a general correspondence of the orders is evident and the agreement between systems 1 and 8a is very good.

TABLE III
EFFICIENCIES OF END GROUPS IN PROMOTING NEMATIC MESOMORPHISM IN SYSTEMS 1, 7, 8a, 8b AND SCHIFF BASE–AZOXYANISOLE MIXTURES

System	Ref	Group efficiencies
1		MeO > NO_2 > Br ~ *n*-PrO ~ Cl > Me > *n*-$C_5H_{11}O$ > F > H
7	6a	MeO > NO_2 > Cl > *n*-$C_5H_{11}O$[a] > F > H
8a	22	MeO > NO_2 > *n*-PrO ~ Cl ~ Br > Me > *n*-$C_5H_{11}O$ > F > H
8b	22	MeO > *n*-PrO > *n*-$C_5H_{11}O$ > Me ~ NO_2[b]
Mixtures	21	NO_2 > MeO > Cl = Me > Br ~ H

[a] The $C_5H_{11}O$ ester has not been reported, but this position for it is assured from interpolation between the known C_4H_9O and $C_6H_{13}O$ esters. [b] This position is questionable since the compound decomposed at the N–I transition temperature.

The use of data from a systematic structural modification study of one nematic molecular system as a guide to other systems can be rewarding. Certainly, the discovery of Kelker, *et al.*,[13a] that the *n*-butyl end group lowers the melting points of nematic Schiff bases and the demonstration by Arora, *et al.*,[7] that a methyl substituent on the central phenylene ring of type 1 esters has a similar effect have been applied to other systems with outstanding success.[9,13b,14–19] The correlations presented in this paper are further evidence that this approach is highly worthwhile.

Registry No.—2 (R = H), 2444-19-1; 2 (R = *i*-Pr), 40782-20-5; 2 (R = *t*-Bu), 40782-21-6; 2 (R = cyclohexoxy), 40782-22-7; 2 (R = MeO), 28099-28-7; benzoyl chloride, 98-88-4; *p*-methylbenzoyl chloride, 874-60-2; *p*-methoxybenzoyl chloride, 100-07-2; *p*-isobutoxybenzoyl chloride, 40782-45-4; *p*-hexyloxybenzoyl chloride, 39649-71-3; *p*-(2-ethoxyethoxy)-benzoyl chloride, 40782-47-6; *p*-cyclohexoxybenzoyl chloride, 36823-91-3; *p*-bromobenzoyl chloride, 586-75-4; *p*-cyanobenzoyl chloride, 6068-72-0; *p*-nitrobenzoyl chloride, 122-04-3; *p*-chlorobenzoyl chloride, 122-01-0; *p*-butoxycarbonylbenzoyl chloride, 39853-28-6; *p*-*tert*-butylbenzoyl chloride, 1710-98-1; *p*-isopropylbenzoyl chloride, 21900-62-9; *p*-octyloxybenzoyl chloride, 40782-53-4; *p*-heptyloxybenzoyl chloride, 40782-54-5; *p*-fluorobenzoyl chloride, 403-43-0; *p*-propoxycarbonylbenzoyl chloride, 40782-56-7; *p*-pentyloxybenzoyl chloride, 36823-84-4; *p*-butoxybenzoyl chloride, 33863-86-4; *p*-propoxybenzoyl chloride, 40782-58-9; *p*-ethoxybenzoyl chloride, 16331-46-7; *p*-ethoxycarbonylbenzoyl chloride, 27111-45-1; *p*-methoxycarbonylbenzoyl chloride, 7377-26-6; *p*-isobutoxybenzoic acid, 30762-00-6; *p*-cyclohexoxybenzoic acid, 139-61-7; *p*-(2-ethoxyethoxy)benzoic acid, 40782-64-7; ethyl *p*-hydroxybenzoate, 120-47-8; hydroquinone, 123-31-7.

The Reversible Addition of Hydroxide to Substituted Benzaldehydes

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The equilibrium constants determined for the addition of hydroxide ion to a series of benzaldehydes, mono- and disubstituted in the meta and para positions, can be correlated with $\Sigma\sigma$, with a slope ρ = 2.24. From this the stabilization energy of the carbonyl group of benzaldehyde relative to acetaldehyde can be calculated as 2.7 kcal/mol. For benzaldehydes substituted in one ortho position a linear relationship is observed between the equilibrium constants for addition and the pK_a values of the analogous substituted benzoic acids.

Aliphatic aldehydes and some aliphatic ketones undergo a reversible hydration in neutral aqueous solutions to form the *gem*-diol.[1] Aromatic aldehydes are not hydrated to any appreciable extent, owing to the extra resonance stabilization.

However, in basic solutions, mono- and disubstituted benzaldehydes do undergo a reversible addition of hydroxide ion to form the ionized *gem*-diol. In the present work, equilibrium constants for this addition were measured and are discussed for Scheme I, with correlations proposed for the various substituents.

Experimental Section

The substituted benzaldehydes were pure commercial products, recrystallized before use to a constant melting point. The methiodide of 4-dimethylaminobenzaldehyde, prepared by refluxing the amine with methyl iodide, had mp 158° (lit.[2] mp 156–157°).

Uv spectra were recorded on a Cary 17 spectrophotometer, and the pmr spectra on a Jeol C-60HL instrument at 30°; chemical shifts in parts per million are noted downfield relative to the sodium salt of 3-(trimethylsilyl)propanesulfonate.

The amount of hydroxide addition was followed by uv spectroscopy at 25°, by observing the instant decrease of the aromatic carbonyl band on addition of base. The spectra were recorded at various concentrations of base until the intensity decreased to a constant value, with formation of a new band. For all the benzaldehydes substituted with one or two chlorines only, the final absorption approached or was extrapolated to zero. For the unsubstituted and 2-CH_3 benzaldehydes, only 10–20% hydroxide addition was determined, and the absorption of the *gem*-diol form was taken as zero. The ratio of hydroxide adduct to carbonyl compound is shown in eq 1, where OD_0 is the carbonyl

$$\frac{[\text{C(OH)(O}^-\text{)}]}{[\text{C=O}]} = \frac{OD_0 - OD_{OH}}{OD_{OH} - OD_{final}} \qquad (1)$$

absorption in neutral solution and OD_{OH} is the absorption at some hydroxide concentration. These values were plotted *vs.* the hydroxide ion concentration, the slope of the line being K_{OH}, with intercepts through the origin. As shown, some of the carbonyl compounds are hydrated to a small extent in neutral solution, and OD_0 is the carbonyl absorption in the presence of of the *gem*-diol. However, the same procedure for K_{OH} is valid.

The amount of initial hydration as shown directly by nmr for 4-trimethylammonium benzaldehyde iodide and indirectly for 3-nitrobenzaldehyde (see Results and Discussion) is not more than 10%. As small amounts of *gem*-diol are difficult to deter-

(1) R. P. Bell, *Advan. Phys. Org. Chem.*, **4**, 1 (1966).
(2) G. R. Wiley and S. I. Miller, *J. Org. Chem.*, **37**, 767 (1972).

TABLE I
EQUILIBRIUM CONSTANT DETERMINATIONS

Registry no.	Substituted benzaldehyde	λ_{max}[a] (ϵ)[b]	Range of [OH^-] (c)	K_{OH}[d]
100-52-7	3,4-H_2	250 (13,900)	0.36–1.0 (3)	0.18
104-88-1	4-Cl	260 (17,900)	0.20–1.3 (4)	0.47
587-04-2	3-Cl	249 (10,800)	0.13–0.80 (5)	1.13
6287-38-3	3,4-Cl_2	260 (12,800)	0.03–0.90 (7)	2.5
24964-64-5	3-CN	245 (9,900)	0.03–0.50 (6)	4.8
7541-76-6	4-N^+Me_3	230 (22,000)	0.01–0.33 (6)	7.6
10203-08-4	3,5-Cl_2	252 (8,250)	0.03–0.30 (6)	7.7
99-61-6	3-NO_2	233 (19,300)	0.03–0.50 (7)	8.3
555-16-8	4-NO_2	268 (11,450)	0.017–0.30 (6)	13.3
16588-34-4	3-NO_2-4-Cl	245 (19,600)	0.005–0.08 (7)	21
529-20-4	2-CH_3	254 (7,500)	0.65–1.3 (3)	0.095
89-98-5	2-Cl	253 (11,400)	0.067–1.0 (7)	2.6
874-42-0	2,4-Cl_2	264 (12,100)	0.03–0.50 (9)	6.0
83-38-5	2,6-Cl_2	255 (5,800)	0.017–0.50 (7)	10.8
552-89-6	2-NO_2	225 (12,600)	0.01–0.30 (6)	15
6361-22-4	2-Cl-6-NO_2	260[e] (5,250)	0.01–0.06 (5)	36
6361-21-3	2-Cl-5-NO_2	240 (9,800)	0.003–0.03 (4)	62
528-75-6	2,4-$(NO_2)_2$	246 (14,500)	0.0008–0.02 (4)	215

[a] Wavelengths at which absorption was studied. [b] Extinction coefficients are from one sample weighing. [c] Number of points on plot. [d] $K_{OH} = [>C(OH)O^-]/[>C{=}O][OH^-]$ at 25°. [e] Shoulder.

mine accurately by nmr or uv,[3] it can be assumed that other aldehydes with electron-withdrawing substituents have similar small degrees of hydration. For the 2,6-dichloro- and 2-chloro-6-nitrobenzaldehydes, the extinction coefficient is appreciably lower than for the other aldehydes and thus the possibility of hydration arises. It was found, however, that the extinction coefficient of these compounds in organic solvents is even smaller than in water. This served as evidence against hydration in neutral solutions. The extinction coefficients and band shapes for 2,4-dinitrobenzaldehyde were the same in water and the organic solvents acetonitrile, dioxane, and chloroform, and the possibility of some hydration exists.

The addition of base was reversible and by neutralizing the basic solutions, the original spectra were obtained.

Changes in the spectra in basic solutions due to other reactions were checked for, and did not interfere during the time of the experiment.

At base concentrations above 1.5 *M*, the ratio of [ionized *gem*-diol]/[carbonyl] was no longer linear with base, presumably owing to a change in the activity of water in these concentrated solutions, where the proper acidity functions should be used.

The ionic strength was not kept constant in the determination of K_{OH}. In a few cases K_{OH} was measured at μ 1.0 with KCl. The values were 10–15% lower than those presented in Table I. It was therefore assumed that the salt effect on the equilibria would not be of such magnitude as to affect the logarithmic correlations.

Results

In Table I are listed the substituted benzaldehydes studied and the experimental results.

At room temperature and in the range of base concentrations studied (0.01–1.3 *M*), no other reactions, such as the Cannizzaro disproportionation or the cleavage of 2,6-dihalobenzaldehydes to 1,3-dihalobenzenes and formate ion, occur. The latter reaction was studied by Bunnett, *et al.*,[4] who observed the reversible addition of hydroxide.

It has been shown in nmr studies that the aldehydic protons shift to higher fields when the carbonyl group adds water to form the *gem*-diol.[1,5] The difficulty in the present case was the limited solubility of the substituted benzaldehydes in water, usually not sufficient for running the nmr spectra. An exception was the soluble 4-trimethylammoniobenzaldehyde iodide. A 0.50 *M* solution in D_2O showed, in addition to the expected three lines at δ 10.22, 8.24, and 3.84, a small peak at δ 6.2 and a small structured line 0.34 ppm upfield from the aromatic line.[6] These small lines were not observed in DMSO-d_6 as solvent, and were ascribed to the protons of the *gem*-diol compound. Integration and comparison of the aldehydic hydrogen and the hydrogen bound to the *gem*-diol group at δ 10.22 and 6.2, respectively, as well as the two aromatic lines at 8.24 and 7.90 ppm, showed that approximately 10% of the compound was hydrated in D_2O solution. As hydroxide was added to the solution, the aldehyde peak as well as the *gem*-diol hydrogen both shifted and broadened owing to a fast exchange between the species.

In concentrated hydroxide solution the solubilities of the substituted benzaldehydes increased owing to the ionization of the *gem*-diol formed. The nmr spectrum of 2-nitrobenzaldehyde in 1 *M* base had no peak in the range of aldehydic protons. However, a broad line appeared at δ 6.5 ppm, ascribed to the hydrogen bound to the ionized *gem*-diol group.

Discussion

The addition of hydroxide to the substituted benzaldehydes can be viewed as a reversible attack of water which is favored in basic solutions owing to the ionization of the *gem*-diol formed. In Scheme I and eq 2, it is shown that K_{OH} is a composite of K_{H_2O} and K_a, where K_{OH} and K_{H_2O} are defined as association constants and K_a and K_w as dissociation constants of the acids (and include the concentration of water).

Correlation of the Meta- and Para-Substituted Benzaldehydes.—For the series of benzaldehydes, mono- and disubstituted in the 3 and 4 positions, there exists a good correlation with $\Sigma\sigma$, the sum of the aro-

(3) P. Greenzaid, Z. Rappoport, and D. Samuel, *Trans. Faraday Soc.*, **63**, 2131 (1967).

(4) J. F. Bunnett, J. H. Miles, and K. V. Nahabedian, *J. Amer. Chem. Soc.*, **83**, 2512 (1961).

(5) P. Greenzaid, Z. Luz, and D. Samuel, *J. Amer. Chem. Soc.*, **89**, 749 (1967).

(6) The aromatic line for this compound had very little structure, as expected for an AA'BB' pattern, pointing to similar chemical environments for the aromatic protons.

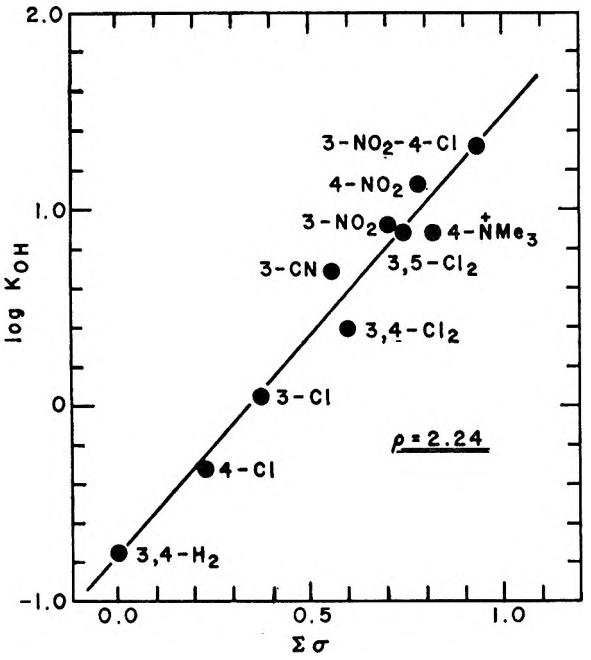
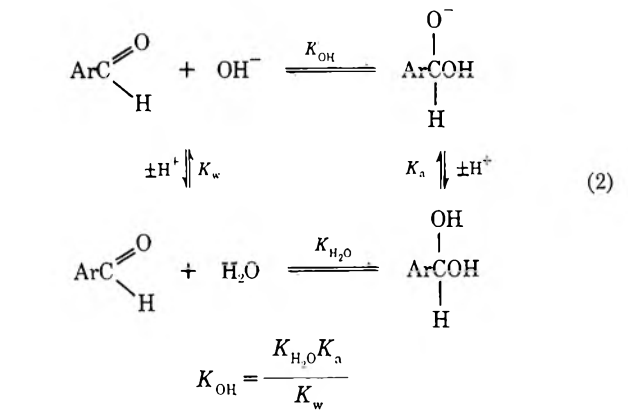


Figure 1.—Plot of log K_{OH} for hydroxide addition to substituted benzaldehydes *vs.* $\Sigma\sigma$, the sum of the aromatic substituent constants.



matic substituent constants[7] (Figure 1). The slope of the plot (ρ_{OH}) is 2.24 with a correlation coefficient of 0.982.

From eq 2

$$\rho_{OH} = \rho_{H_2O} + \rho_{K_a} \quad (3)$$

It was shown that the pK_a values of the *gem*-diols of a series of substituted trifluoroacetophenones are correlated with σ values[8] with ρ = 1.11. Taking ρ_{K_a} = 1.1 for the dissociation of the *gem*-diols of substituted benzaldehydes, from eq 3, ρ_{H_2O} = 1.1 for the hydration equilibria. Relative to the dissociation of carboxylic acids (ρ = 1.0), these values are similar to those found for aliphatic compounds where $\rho^*_{K_a}$ = 1.32,[9] $\rho^*_{H_2O}$ = 1.70,[5] and for the acid dissociation[10] ρ^* = 1.62.

pK_a and K_{H_2O} Values.—The pK_a values for the substituted benzaldehyde hydrates can be evaluated from those determined for the substituted trifluoroacetophenone hydrates.[8] Of interest here are the reported values of 9.2 for the 3-nitro derivative and 10.0 for the unsubstituted compound. Using $\rho^*_{K_a}$ = 1.32 and inserting σ^*_H for $\sigma^*_{CF_3}$, the corresponding pK_a's for the aldehyde hydrates can be derived: for the *gem*-diol of 3-nitrobenzaldehyde, pK_a = 12.0, and for the unsubstituted benzaldehyde hydrate, pK_a = 12.8.

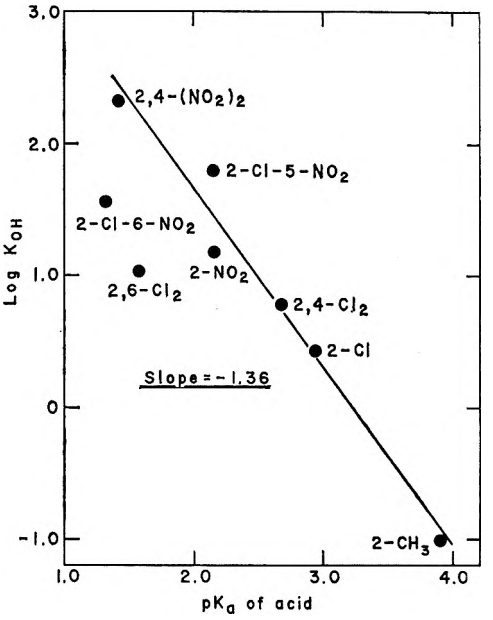


Figure 2.—Plot of log K_{OH} for hydroxide addition to 2-substituted benzaldehydes *vs.* the pK_a values[16] of the analogous benzoic acids.

From eq 2, using the calculated pK_a and the measured K_{OH} values for 3-nitrobenzaldehyde, the value of K_{H_2O} is 0.08. Therefore this compound is slightly hydrated in neutral solution, although less than 10%. For the unsubstituted benzaldehyde K_{H_2O} is calculated to be 1.1×10^{-2}.

Resonance Stabilization of the Aromatic Carbonyl.—From the correlation of K_{H_2O} for the aliphatic compounds,[5] using σ^* = 0.60 for the phenyl group,[11] the calculated equilibrium constant for hydration of benzaldehyde equals 11.2. This value is higher than that calculated previously, as only the inductive effect of the benzene ring is taken into account without the conjugative interaction with the carbonyl group. In terms of free energy, this means that the additional stabilization of the carbonyl of benzaldehyde is 4.1 kcal/mol, relative to an aliphatic aldehyde with a group of similar inductive effect as the phenyl ring (assuming no extra-stabilization of the phenyl ring in the addition product). Relative to acetaldehyde, this stabilization amounts to 2.7 kcal/mol.

In a similar fashion, from the addition of other nucleophiles, Fersht[12] estimated the extra stabilization of the aromatic carbonyl in benzaldehyde compared to acetaldehyde as 4 ± 0.4 kcal/mol. The classical method of evaluating the extra resonance energy of the aromatic carbonyl is from bond dissociation energies and Pauling's calculated value[13] is 4 kcal/mol. However, the relative error in such a treatment is large, as large amounts of energy are subtracted to give a small difference.

(7) D. H. McDaniel and H. C. Brown, *J. Org. Chem.*, **23**, 420 (1958).
(8) R. Stewart and R. Van der Linden, *Can. J. Chem.*, **38**, 400 (1960).
(9) J. Hine and G. F. Koser, *J. Org. Chem.*, **36**, 1348 (1971).
(10) G. B. Barlin and D. D. Perrin, *Quart. Rev., Chem. Soc.*, **20**, 75 (1966).
(11) (a) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 13; (b) S. Takahashi, L. A. Cohen, H. K. Miller, and E. G. Peake, *J. Org. Chem.*, **36**, 1205 (1971).
(12) A. R. Fersht, *J. Amer. Chem. Soc.*, **93**, 3514 (1971).
(13) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 198.

Ortho-Substituted Benzaldehydes.—For benzaldehydes substituted in the ortho position, a similar correlation could not be shown as there is no reliable set of ortho-substituent constants.[14,15] A correlation does exist, however, for values of K_{OH} for six benzaldehydes substituted in only one of the ortho positions, with the pK_a values[16] for the analogous substituted benzoic acids with a slope of −1.36 and correlation coefficient 0.984 (Figure 2). This correlation is limited to compounds with only one ortho position substituted, as the two compounds with substitution at both ortho positions deviate markedly. 2,4,6-Trimethylbenzaldehyde also deviates from the plot, as there was no indication of addition up to 1 *M* base, while the pK_a value for the corresponding acid is 3.44. A similar deviation of di-ortho substitution was noted when correlating the rate constants for the attack of diphenyldiazomethane on ortho-substituted benzoic acids in ethanol, with the pK_a's of the acids.[17]

Acknowledgment.—Discussions with W. P. Jencks and R. P. Bell are gratefully acknowledged.

(14) J. Shorter in "Advances in Free Energy Relationships," N. B. Chapman and J. Shorter, Ed., Plenum Press, London, 1972, p 72.
(15) M. Charton, *Progr. Phys. Org. Chem.*, **8**, 235 (1971).
(16) J. F. J. Dippy and S. R. C. Hughes, *Tetrahedron*, **19**, 1527 (1963).
(17) N. B. Chapman, J. Shorter, and J. H. P. Utley, *J. Chem. Soc.*, 1824 (1962).

Free-Radical Addition of Iodoperfluoroalkanes to Terminal Alkadienes. Relative Reactivity as a Function of Chain Length and Reaction Conditions[1,2]

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Terminal alkadienes, $CH_2{=}CH(CH_2)_nCH{=}CH_2$ (n = 1–4, 1 to **4**), gave mono- and bisadducts from iodoperfluoroalkanes (R_FI) in high yield. 1,6-Heptadiene (**3**) was unusual in preferentially cyclizing under conditions which favored linear adducts from the other dienes. For **3** the ratio of linear to cyclic adducts was dependent on R_FI concentration, as predicted from kinetic analysis of the reaction scheme. Relative reactivities on an equivalent double-bond basis for alkadienes against either 1-hexene or 1-heptene were the following: **1**, 0.935; **2**, 0.805; **3**, 1.08–1.42, depending on reaction conditions; **4**, 0.945. Thus, only **3** reacted significantly faster than an alkene on the basis of available reaction sites, and this appears to be related to cyclization of **3**. The overall results are interpreted as being dependent on radical intermediate conformations. The absence of significant amounts of cyclization products from **2** or **4**, or of isomeric adducts of the structure $ICH_2CHR_F(CH_2)_nCH{=}CH_2$ (n = 1–4), has been confirmed for azonitrile-initiated reactions.

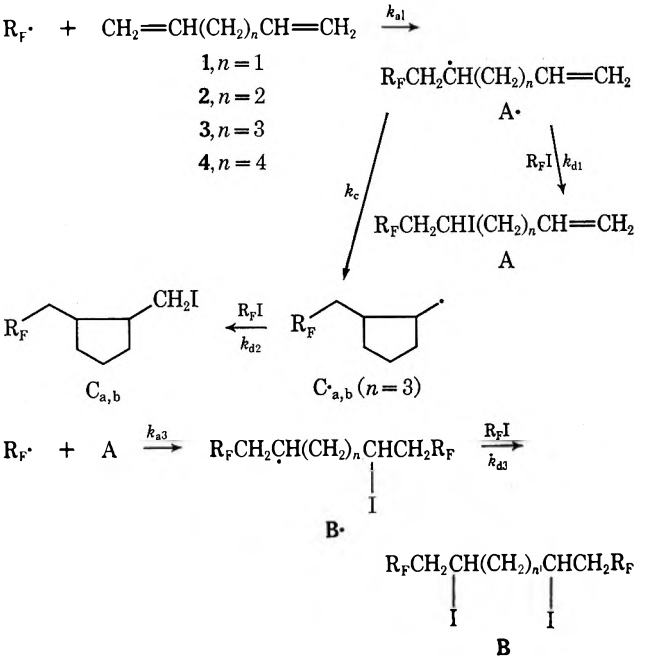
In previous work[3–5] it was found that 1,6-heptadiene (**3**) and substituted 1,6-heptadienes cyclized to *five-membered* ring compounds during the addition of free radicals from perfluoroalkyl iodides (R_FI), carbon tetrachloride, chloroform, and the like. 1,5-Hexadiene (**2**) or 1,7-octadiene (**4**) did not cyclize under free-radical conditions, however, but gave open-chain adducts in excellent yield. By contrast, R_FI and 1,3-butadiene reacted poorly, probably because an unstable product was formed.[6] (Styrene gave an adduct of analogous structure which also was exceedingly sensitive to heat, light, and air.)[7,8] As part of a continuing study of R_FI reactions it seemed worthwhile to determine the relative reactivity of terminal alkadienes, and to look more carefully into the matter of their propensity to cyclize.[9] Quantitative comparison with norbornadiene, which also cyclized with great ease,[10] was desired. It was felt that these data would shed some further light on the nature of these interesting free-radical processes.

(1) Presented in part at the Fourth European Symposium on Fluorine Chemistry at Ljubljana, Yugoslavia, September 1972.
(2) See paragraph at end of paper regarding supplementary material.
(3) N. O. Brace, *J. Amer. Chem. Soc.*, **86**, 523 (1964).
(4) N. O. Brace, *J. Org. Chem.*, **31**, 2879 (1966).
(5) N. O. Brace, *ibid.*, **32**, 2711 (1967).
(6) N. O. Brace, U. S. Patent 3,145,222, assigned to E. I. du Pont de Nemours and Co., Aug 18, 1964.
(7) N. O. Brace, *J. Org. Chem.*, **27**, 3033 (1962).
(8) N. O. Brace, unpublished observations.
(9) E. S. Huyser, "Free Radical Chain Reactions," Wiley-Interscience, New York, N. Y., 1970, pp 182–185. Cyclizations of 1,7-octadiene and of 1,5-hexadiene during addition of CCl_4 are reported, but neither references to the original literature nor supporting evidence were given.
(10) N. O. Brace, *J. Org. Chem.*, **27**, 3027 (1962).

Results

Reactions of R_FI with alkadienes **1**–**4** are outlined in Chart I. The yield of monoadduct A, bisadduct

CHART I
REACTION OF R_FI WITH DIENES



B, or cis and trans cyclic adducts $C_{a,b}$ varied with reaction conditions.

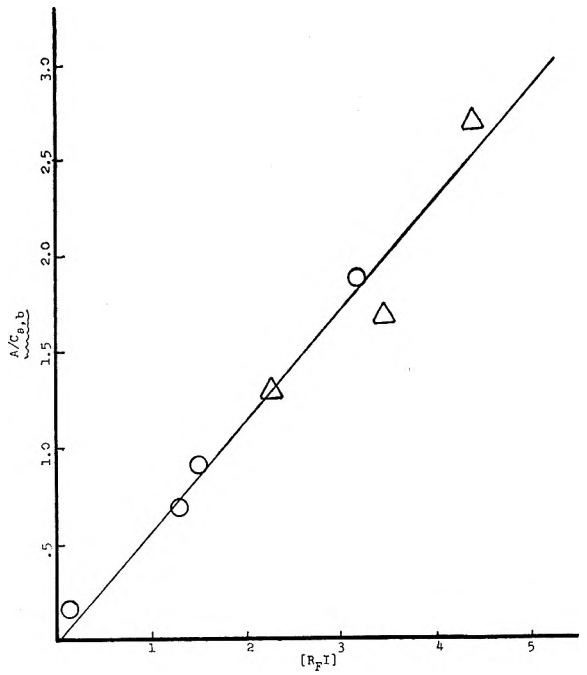


Figure 1.—Dependence of $A/C_{a,b}$ on R_FI concentration: Δ, mol/l. of $CF_3CF_2CF_2I$ and **3**; ○, **5**, **3**, and **6** (see Table I.)

Kinetic analysis of the reaction scheme given in Chart I, as employed by Carlsson and Ingold[11] or by Kochi and Powers[12] in somewhat analogous systems, predicts that the A to $C_{a,b}$ ratio should be proportional to R_FI concentration.

$$\frac{A}{C_{a,b}} = \frac{k_{d1}}{k_c}[R_FI]$$

The available data are consistent with this prediction, which assumes that k_{d1} and k_{d2} are of comparable value.[13] The A to $C_{a,b}$ ratio from reaction of R_FI with 1,6-heptadiene (**3**) at 70° (extrapolated to zero time) in seven sets of experiments are recorded in Table I and plotted in Figure 1. Reactions were all initiated

TABLE I

EFFECT OF R_FI CONCENTRATION ON $A/C_{a,b}$ AT 70°

—$CF_3(CF_2)_nI$—		Mol of	
n	mol/l.	$A/C_{a,b}$	Source of data
2	2.29[a]	1.3	Ref 4
2	3.50[a]	1.7	Ref 4
2	4.44[a]	2.7	Ref 4
3	0.140	0.18	Table VII, runs 6–8
3	1.32	0.70	Table VII, runs 1–4
3	1.47	0.92	Table X, part 3
3	3.21	1.9	Table X, part 1

[a] $CF_3CF_2CF_2I$ and **3** only were present.

by azobis-2-methylpropionitrile (ABN), but under different conditions. The data for runs using $CF_3CF_2CF_2CF_2I$ (**5**) were obtained in competitive experiments in which 1-hexene (**6**) was also present; details are given below.

A second pathway to $C_{a,b}$ also exists, as a slow isomerization of A to $C_{a,b}$ occurs during reaction and subsequent to the addition of R_FI.[4] This can be seen from Figure 2. Under these reaction conditions (with excess diene) little B was formed, but $C_{a,b}$ continued to increase after all the R_FI was gone (41% of R_FI had reacted in 1 hr and 99.7% in 4 hr). It is significant that the trans isomer of C was formed about five or six times faster than cis C. Isomerization of A to $C_{a,b}$ and radical rearrangements of related compounds have been independently observed.[5]

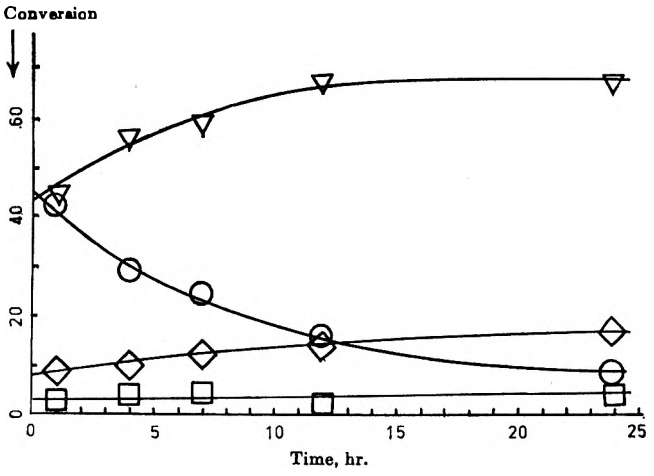


Figure 2.—Reaction of 1-iodoperfluoropropane and **3** at 70° (ref 4): $CF_3CF_2CF_2I$, 5.00 mmol; **3**, 10.00 mmol; ABN, 0.100 mmol. ▽, trans C_b; ○, monoadduct A; ◇, cis C_a; □, bis adduct B.

It was interesting to observe the effect of R_FI/diene ratio on mono- and bisadducts from reaction of **5** with these alkadienes. As shown in Table II, the highest A/B ratios were found with **1**, **2**, and **4** when an excess of diene was present; with **3**, however, *cyclization* to $C_{a,b}$ was the predominant reaction. Even in the presence of an excess of R_FI much of **3** cyclized, while the other dienes gave mostly B. As previously reported[4] for **2** and **4**, it is now found that also with **1** linear adducts are obtained under all conditions. Careful examination of product mixtures from all these dienes by gas–liquid partition chromatography (glpc) showed two or three impurities at the 1–2% level. In reaction mixtures of **4** there were found two additional products which appeared at the retention times anticipated for cyclic isomers.

TABLE II

EFFECT OF REACTANT RATIO ON MONO- AND BISADDUCTS FROM $CF_3CF_2CF_2CF_2I$ (**5**) AND ALKADIENES[a]

Diene	Mol of 5/diene	Convn of diene or 5, %	Mol of A/B
1	0.250	86	12.7
	4.00	76	0.410
2	0.250	76	11.5
	2.00[b]	96	0.60[b]
	2.50	95	0.25
3	0.250	81	*c*
	2.00	83	1.54[d]
4	0.250	82	16.1
	0.500	44	10.1
	2.00[b]	97	0.67[b]
	2.10	95	0.672

[a] All reactions were done at 70.0° in a sealed tube, using ABN as initiator; see Table III for details. [b] See ref 4. [c] Reaction gave 1.5% of A, less than 2% of B, and 80% of $C_{a,b}$. [d] There was formed also 35.2% of $C_{a,b}$.

(11) D. J. Carlsson and K. U. Ingold, *J. Amer. Chem. Soc.*, **90**, 7047 (1968).

(12) J. K. Kochi and J. W. Powers, *ibid.*, **92**, 137 (1970).

(13) It has been shown that cyclization in this system is not reversible[11] as ring opening of the cyclopentylmethyl radical does not occur.[14]

(14) R. C. Lamb, P. W. Ayers, and M. K. Toney, *J. Amer. Chem. Soc.*, **85**, 3483 (1963).

TABLE III

PREPARATION OF ADDUCTS FROM $CF_3CF_2CF_2CF_2I$ (5) AND TERMINAL ALKADIENES AT 70°[a]

Diene	Mol	5/diene	ABN, mmol	Time, hr	Yield, % A	Yield, % B	Yield, % C	Physical constants A Bp, °C (mm)	Physical constants A $n^{25}D$	Physical constants B Bp, °C (mm)	Physical constants B $n^{25}D$
1	0.100	0.250	2.00	16	74	12		68 (11)	1.3967	82 (0.10)	1.4050
1	0.0250	4.99	1.00	8.5	22.1	53.5					
2	0.200	0.250	1.82	9.5	65	11[b]		85 (12)	1.4010	79 (0.30)	1.4350
2	0.0200	2.50	2.00	6	20	79.2					
3	0.200	0.250	0.92	4	1	(2)	80[c]	90 (8)	1.4065		
3	0.100	2.00	0.92	1	28.9	18.8	35.2			108 (0.25)	1.4091
3	0.0250	2.00	0.50	16[d]	30.8	8.06	34.1				
4	0.200	0.250	1.00	18	72	(10)		57 (0.25)	1.4090		
4	0.200	0.500	2.00	16	38	(7.6)					
4[e]	0.0500	2.00	1.00	18	21	76		50 (0.25)[e]	1.4080[e]	115 (0.20)[e]	1.4100[e]
4	0.105	2.10	1.50	9	38.2	52.9					

[a] Satisfactory analytical data (±0.4% for C, H, F, or I) were reported for all new compounds listed in the table. [b] Moles times two since 2 mol of 5 used, limiting reactant. [c] C (n = 3), bp 69° (0.75 mm), $n^{25}D$ 1.4186. [d] Reaction temperature was 130°. [e] Reference 4.

The amount was too small, however, to warrant trapping for identification. The other isomers are probably of the type $ICH_2CHR_F(CH_2)_nCH{=}CH_2$ (n = 1, 2, or 4), as previously indicated for the addition of CF_3I to 1-heptene[15] (7) and now confirmed by others[16,17] for R_FI additions in similar cases. The amount of these isomers varied with reaction conditions, as it has been shown[17] that the linear adduct is favored by kinetic control. Rearrangement to the branched isomer has been demonstrated in one case.[17]

Details for the preparation of adducts, their physical properties, and analytical data are given in Tables III and IV. Characteristic infrared and nmr spectral properties are listed in the Experimental Section. The nmr spectrum of $C_4F_9CH_2CHI(CH_2)_3CH{=}CH_2$, A ($n$ = 3) is presented as Figure 3;[2] significant features of the linear adduct structure are clearly evident from the spectrum. The nmr spectrum of the 1-hexene adduct $C_4F_9CH_2CHI(CH_2)_3CH_3$ appears as Figure 4.[2] Spectral evidence is in full accord with the postulated structure. In both instances proton resonances for CHI at δ 4.4 and for R_FCH_2 at δ 2.8 have the correct areas and splitting patterns.

Relative Reactivities.—A reference olefin, 1-hexene (6) or 1-heptene (7), competing for 5 with another unsaturated compound, gave valid results when the reaction was conducted and the products analyzed as previously described.[15] Two different reference olefins were required to avoid overlapping of peaks in glpc analysis of 1–4. This technique was recently applied to the determination of relative reactivities of a series of cyclic olefins.[18] It was not sufficient merely to follow the disappearance of olefin, as a small change in concentration was difficult to determine accurately; and as shown above, several products may be formed from the same starting material. Because of the disparate nature of the reactants and products, correction factors varied with composition of a mixture. Factors were therefore determined for more than one mixture of 3, and in every case for a standard mixture similar in composition to unknown samples. Quantitative aspects of radical additions to olefins have been critically reviewed by Cadogan and Sadler.[19]

The method was applied to reaction of 5 with several pairs of alkenes (Tables V and VI).[2] 1-Hexene (6) against 1-heptene (7) gave initial and final reactivity ratios of 6/7 of 1.03 ± 0.02. The reactivity ratio for norbornene (8) against 7 was redetermined using the technique of this study; the two values (1.0[15] and 1.00) were identical. Norbornadiene (9) against 7 gave 9/7 of 1.83 ± 0.01. The diene series 1–4 was compared against either 6 or 7 for different reaction times and reactant ratios, particularly with 2 and 3 to ascertain what effect these variables might have on reactivity ratios. These data are collected in Tables VI[2] and VII, and summarized in Table VIII. Results for 3 are given separately because of their unique nature.

Discussion

Chart I summarizes the various reaction steps to be discussed. Termination reactions of the usual kind are assumed to account for the radical chain. These would result in the coupling of R_F radicals, of A·, B·, and $C_{a,b}$· radicals and probably in allylic termination reactions as previously observed.[4,10,15]

Relative reactivity $\bar{P}$ of two alkenes toward addition of R_F radicals is given by the usual equation[19,20]

$$\bar{P} = \frac{\log ([M_1]_0/[M_1]_f)}{\log ([M_2]_0/[M_2]_f)} = \frac{k_{a1}}{k_{a2}}$$

for competitive reactions, where $[M_1]_0$ and $[M_1]_f$ are initial and final concentrations of olefin M_1, and $[M_2]_0$ and $[M_2]_f$ are initial and final concentrations of M_2. It was advantageous, for analytical reasons, to substitute for $[M_1]_f$ the equivalent quantity ($[M_1]_0$ − [products]) in determining $\bar{P}$, as has been done by others.[17,19]

As summarized in Table VIII, 1,5-hexadiene appears to be significantly less reactive than the other dienes, but the difference in the remaining compounds is not great. The variation of adduct formation with time (extent of conversion) shown in Figure 2 was observed in reactions of 3 with R_FI at different reactant ratios. The reactivity ratio, however, varied only slightly as a function of R_FI conversion or $A/C_{a,b}$

(15) N. O. Brace, *J. Org. Chem.*, **28**, 3093 (1963).
(16) M. Capka and V. Chvalovsky, *Collect. Czech. Chem. Commun.*, **33**, 2872 (1968).
(17) R. N. Haszeldine, D. W. Keen, and A. E. Tipping, *J. Chem. Soc. C*, 414 (1970).
(18) N. O. Brace, *J. Org. Chem.*, **37**, 2429 (1972).
(19) J. I. G. Cadogan and I. H. Sadler, *J. Chem. Soc. B*, 1191 (1966).
(20) E. S. Huyser, "Free Radical Chain Reactions," Wiley-Interscience, New York, N. Y., 1970, p 61.

TABLE VII

COMPETITION REACTIONS OF $CF_3CF_2CF_2CF_2I$ (5) WITH 1,6-HEPTADIENE AND 1-HEXENE

Run no.	Time, hr	5, initial mmol	Alkene1 1,6-Heptadiene (3) mmol Reactant	A	B	C	Convn % of 5	Alkene2 1-Hexene (6) mmol Reactant	Product	Convn % of 5	$\frac{A}{C_{a,b}}$	$\frac{k_1}{k_2}$
1	0.083	4.8800[a]	10.025	0.2133		0.3386	11.31	9.944	0.2676	5.48	0.630	2.145
2	0.167	4.8800	10.025	0.9628	0.0382	1.8248	57.90	9.944	1.4124	28.94	0.5488	2.162
3	0.33	4.8800	10.025	0.6900	0.0384	1.601	47.70	9.944	1.173	24.04	0.4596	2.105
4	1.00	4.8800	10.025	0.7197	0.0589	2.238	61.80	9.944	1.525	31.24	0.3479	2.196
5	1.00	4.8800	10.025	0.6731	0.0473	2.370	63.30	9.944	1.508	30.90	0.3090	2.185
											Mean	2.159
												= 0.040
6	1.16	1.2236[b]	10.1466	0.0793		0.4861	45.76	10.379	0.2657	21.71	0.1520	2.359
7	4.16	1.2236	10.1466	0.0509		0.6826	59.95	10.379	0.2713	22.17	0.07457	2.836
8	7.00	1.2236	10.1466	0.0504		0.6392	52.24	10.379	0.2306	18.85	0.0788	3.134[c]

[a] $[R_FI] = 1.32$. [b] $[R_FI] = 0.140$. [c] Owing to a decrease in adducts from both alkenes, this value is uncertain. See, however, Table X for a similar value from another experiment.

TABLE VIII

RELATIVE REACTIVITY OF ALKENES AND DIENES WITH $CF_3CF_2CF_2CF_2I$ (5) AT 70°

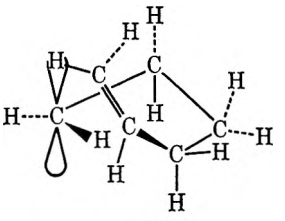
Olefin pair	$\bar{P}$	$\bar{P}$/ double bonds
6/7	1.03 ± 0.02	1.03 ± 0.02
8/7	0.996 ± 0.005	0.996 ± 0.005
9/7	1.83 ± 0.01	0.965 ± 0.01
1/7	1.87 ± 0.05	0.935 ± 0.05
2/7	1.61 ± 0.03	0.805 ± 0.03
3/6	2.16 ± 0.04[a]	1.08 ± 0.04[a]
3/6	2.84[b]	1.42[b]
4/6	1.89 ± 0.01	0.945 ± 0.01

[a] At moles of 5/3 = 0.4868. [b] At 5/3 = 0.1206.

ratio (Table VII, runs 1–5). At a low 5/3 reactant ratio of 0.1206 which greatly increased cyclization, $\bar{P}$ increased substantially to at least 2.84 (runs 6–8).

Reactivity ratio $\bar{P}_{\text{diene/alkene}}$ for a diene competing against an olefin should be twice as large as for an alkene, since there is twice the probability that an R_F radical will attack a diene at the same concentration as an alkene.

The reactivity ratio on a *per double bond basis* for dienes 1–4 and 9 shows that only 3 reacted significantly faster than the reference olefin. Models show that effective overlap of the adduct radical A· ($n = 3$) with the π electrons of the terminal double bond is quite possible in at least two staggered conformations. It seems significant that 3 reacted fastest under conditions where cyclization was enhanced. This may mean that rate of radical addition to 3 is increased by overlap to the π bond. While the amount of acceleration was not great, it was clearly present in 3 and not in 2 or in 4. Indeed, it has been recently shown that the 5-hexenyl radical generated at low temperature readily rearranges to the cyclopentylmethyl radical[21–24] and that the esr spectrum of the 5-hexenyl radical exhibits large temperature-dependent changes.[23] The broadening of the β-proton triplets is attributed to coiling of the radical into conformation 10, in which the terminal unsaturated linkage lies over the radical center.[24] This same conformation had been previously postulated by Lamb, Ayers,



10

and Toney[14] as a possible common precursor to cyclization products.[25]

As pointed out by Capon and Rees,[26] cyclization of radical A· ($n = 3$) occurs by a path having a transition state closer in energy to the *open-chain* radical than to the more stable product radical. If overlap with the π electron cloud lowers the activation energy for radical cyclization, this may also reduce the energy required for the R_F· radical to open the original double bond. Hence, the two steps become effectively coupled.

$\bar{P}$ for 4 approached the statistical value of two. Cyclization, if it occurred, was only a minor reaction. It is suggested that entropy of bringing the two ends of the molecule in close proximity is too great to allow such a conformation to affect either the rate of addition of R_F radical or displacement on R_FI. This may also explain the lack of cyclization of 4.

A folded conformation of an alkadiene would offer a certain amount of steric hindrance to the approach of an R_F radical in the rate-determining step. For 1 there is a greater probability that the two ends of the molecule will sweep past each other than for the larger dienes. A model of 1, however, shows that nonbonded repulsion of hydrogens on carbons one and five may be sufficient to restrain such motion and maintain the molecule in a more open conformation. Thus, rate of attack by R_F radical would be less affected.

2 has more degrees of freedom than 1 and attack by the R_F radical may be hindered by proximity of the other terminal double bond. This cannot be due merely to the presence of a four carbon chain residue, since addition to 1-hexene was actually slightly faster than to 1-heptene (Table VIII). Examination of models of 2 shows that there are several staggered conformations which have the terminal double bonds in close proximity. Approach of the R_F radical is

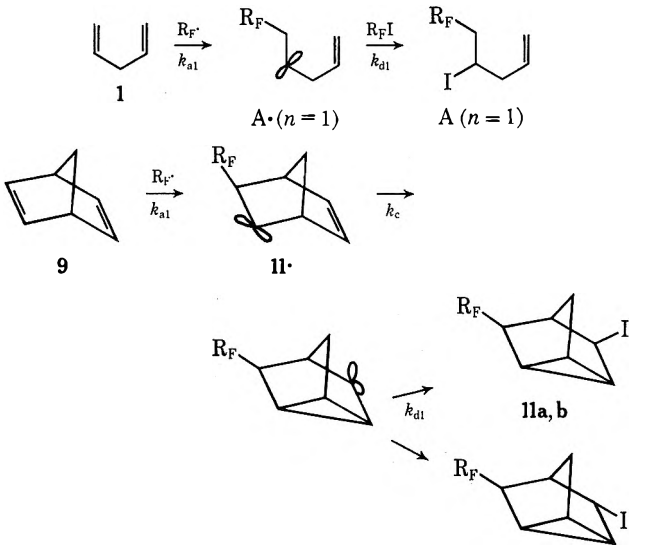
(21) J. K. Kochi and P. J. Krusic, *J. Amer. Chem. Soc.*, **91**, 3940 (1969).
(22) R. A. Sheldon and J. K. Kochi, *ibid.*, **92**, 4395 (1970).
(23) D. J. Edge and J. K. Kochi, *ibid.*, **94**, 7695 (1972).
(24) It was also indicated that such a coiled conformation was not observed for the 3-butenyl radical, although it is known to cyclize.
(25) N. O. Brace, *J. Polym. Sci., Part A-1*, **8**, 2091 (1970).
(26) B. Capon and C. W. Rees, *Proc. Chem. Soc., London*, **61**, 221, 261 (1964).

thought to occur best in the plane perpendicular to the nodal plane[25] and partial blockage of the bulky R_F radical in this orientation could be responsible for the slowing of rate.

The significant difference between the dienes **1** and **9**, both of which are 1,5 dienes, is that the adduct radical **11**· from **9** has the required geometry for facile overlap and cyclization while A· (n = 1) radical does not. This is because addition to **1** occurs predominantly at the end of the double bond and overlap and cyclization would have to form a strained four-membered ring (Chart II).

CHART II

RADICAL INTERMEDIATES IN ADDITION OF R_FI TO 1 AND TO NORBORNADIENE (9)



While **9** cyclized completely it did not react faster than an alkene or even norbornene (**8**) on an equivalent double bond basis (Table VIII). A similar result was reported by Trecker and Henry[27] for relative reactivity of **8** and **9** toward carbon tetrachloride. **9** reacted just twice as fast as **8**, and **9** also cyclized completely to a nortricyclene derivative.

Experimental Section

Sources of Materials and Methods.—Dienes **1–3** and 1-hexene (**6**) came from Chemical Samples Co.; **4** was obtained from Cities Service Co. and was redistilled, bp 117°, $n^{25}D$ 1.4191. **5** was obtained from Thiokol Chemical Co., **7** and **9** from Aldrich Chemical Co., and **8** from Columbia Organic Chemicals Co. The remaining compounds were standard laboratory grade. Glpc analyses of all samples were performed using replicate injections of 1–2 μl on a 6 ft × 0.25 in. column packed with SE-30 silicone oil (10%) on 60–80 mesh Chromosorb W unless otherwise indicated. The column was temperature programmed from 60 to 175° at 20° per minute; the injector was at 150° and the detector at 250°. Helium carrier gas flow of 27 ml/min was used. A Sargent Welch gas chromatograph was fitted with a thermal conductivity detector. Table IX lists the times and weight factors determined for prepared mixtures, using n-octane (**12**), chlorobenzene (**13**), or o-xylene (**14**) as reference compound. In some cases the reference compound was present during reaction.

Infrared spectra were recorded using a Perkin-Elmer Model 337 grating spectrophotometer. Nmr spectra were obtained on a Varian A-60 or T-60 spectrometer. Distillations were performed in a Nester/Faust 2-ft platinum spinning band column (column A).

Competitive Reaction of 6 and 7 with 5.—A mixture was weighed into a tightly capped vial, transferring known volumes of liquids in order of increasing volatility by graduated pipet, starting with chlorobenzene (0.3549 g), **7** (0.9569 g, 9.745 mmol), **6** (0.8339 g, 9.7085 mmol), and **5** (1.9502 g, 5.6371 mmol); a portion (0.3779 g) was removed to prepare a standard mixture (listed in Table IX), and to the remainder (3.7180 g) was added ABN (0.0475 g, 0.288 mmol). The reaction mixture was distributed by capillary pipet while cold into five ampoules made from 8-mm tubing which were evacuated and filled with nitrogen three times at −78° and sealed by hand torch. Four of the ampoules were heated for periods of time at 70.0° as given in Table V. The fifth was opened and analyzed to show that adducts **15** and **16** were not formed during analysis by glpc. The reaction samples were transferred to tightly capped vials and kept cold. Similar techniques were used in the experiments summarized in Tables V, VI, and VII.

Reaction of 5 and 6 to Give 1,1,1,2,2,3,3,4,4-Nonafluoro-6-iododecane (15).—**5** (17.30 g, 0.0500 mol), **6** (4.20 g, 0.0500 mol), and ABN (0.0820 g, 0.500 mmol) were charged to a Fischer-Porter pressure tube, evacuated, and filled three times with nitrogen, sealed and heated for 8 hr at 70°. Distillation gave **15**, bp 81° (10 mm), $n^{25}D$ 1.3942, 15.64 g (72.7%); an oil residue, 0.60 g; and recovered starting materials, 2.40 g; ir ν_{CH} 2950, 2930, 2870, 2860 cm^{-1}; δ_{CH} 1460, 1425, 1375, 1350 cm^{-1}; ν_{CF} 1250–1200, 1130, and bands at 1080, 1020, 1010, 930, 880, 840 (d), 770, 735, 720, and 690 cm^{-1}; nmr (CCl_4) δ 0.90 (3 protons, m, CH_3), 1.1–2.2 [6 protons, $(CH_2)_3$], 2.82 (2 protons, t of d, J_{HF} = 18, J_{HH} = 6 Hz, CF_2CH_2CHI), 4.4 (1 proton, 5 lines, J = 12, 6, 6 Hz, CH_2CHICH_2). The spectrum (Figure 4) conformed to the postulated structure of **15**, and not to an isomeric substance.

Anal. Calcd for $C_{10}H_{12}F_9I$: C, 27.92; H, 2.81; F, 39.76; I, 29.50. Found: C, 27.97; H, 2.77; F, 39.19; I, 29.47.

Reaction of 5 and 7 to Give 1,1,1,2,2,3,3,4,4-Nonafluoro-6-iodoundecane (16).—**5** (17.3 g, 0.0500 mol), **7** (9.82 g, 0.100 mol), and ABN (0.164 g, 1.00 mmol) were charged to a pressure tube and treated as above. After 18 hr at 70° the filtered liquid (26.82 g) gave **16**, bp 95° (10 mm), $n^{25}D$ 1.3982, 17.20 g (77%); an oil residue, 0.57 g; and recovered starting materials, 6.39 g; ir was essentially identical with that of **15**. The nmr spectrum also resembled closely that of **16**, and not that of an isomeric substance.

Anal. Calcd for $C_{11}H_{14}F_9I$: C, 29.75; H, 3.18; F, 38.50; I, 28.57. Found: C, 29.73; H, 3.20; F, 38.22; I, 28.63.

Reaction of 5 with 1 to Give 4-Iodo-6,6,7,7,8,8,9,9,9-Nonafluoro-1-nonene [18 (A, n = 1)].—**5** (8.65 g, 0.0250 mol), **1** (6.81 g, 0.100 mol), and ABN (0.328 g, 2.00 mmol) were processed as above. After 16 hr at 70° the product mixture (16.0 g) gave unreacted **1**, bp 31°, 4.16 g; **18**, bp 68–69° (11 mm), $n^{25}D$ 1.3967, 7.67 g, 74% conversion based on **5**; and an oil residue which glpc showed to contain 11.4% of **18**, an isomer (3.7%) and 49.7% of **19** (B, n = 1). Two higher retention time compounds (14.2 and 21.0%) also were present; ir (**18**) ν_{CH_2} 3080; ν_{CH} 2980, 2920; $\nu_{C=C}$ 1640; ν_{CH} 1430, 1350; ν_{CF} 1250–1200, 1140; bands at 1020, 990, 925, 880, 775, 745, 740, 730, 690, and 515 cm^{-1}. Bands at 990 and 925 cm^{-1} are characteristic for this type of compound; nmr (CCl_4) δ 2.3–3.3 (4 protons, two m, $CF_2CH_2CHICH_2$), δ 4.3 (1 proton, 5 line, J = 13 and 6 Hz, CH_2CHICH_2), 4.9–6.2 (3 protons, m, $CH{=}CH_2$).

Reaction of 5 with 1 to Give 1,1,1,2,2,3,3,4,4,10,10,11,11,-12,12,13,13,13-Octadecafluoro-6,8-diiodotridecane [19 (B, n = 1)].—**5** (34.56 g, 0.100 mol), **1** (1.70 g, 0.0250 mol), and ABN (0.164 g, 1.00 mmol) were treated as above, and heated at 70° for 8 hr. **5** (11.11 g) and trap liquid (8.68 g) were recovered: **18**, bp 64° (9.0 mm), $n^{25}D$ 1.3970, 1.80 g (98.7% by glpc); a mixture of **18** and **19**, bp 57–81° (0.15 mm), 1.62 g (29.5% **18** and 70.5% **19** by glpc); **19**, bp 82° (0.10 mm), $n^{25}D$ 1.4050, 9.04 g (99.5% by glpc); a residue, 0.9 g; ir (**19**), similar to that of (B, n = 4);[4] nmr (CCl_4) δ 2.2 (2 protons, t, J = 6 Hz, $CHICH_2CHI$), 2.2–3.5 [4 protons, m, $(CF_2CH_2CHI)_2$], 4.4, [2 protons, m, $(CHI)_2$].

Reaction of 5 and 3 at 130° to Give 20 (A, n = 3), 21 (B, n = 3), and 22a,b (C, n = 3), Using Di-*tert*-butyl Peroxide Initiator.—**5** (16.4 g, 0.0500 mol), **3** (2.40 g, 0.0250 mol), and di-*tert*-butyl peroxide (0.0685 g, 0.500 mmol) were charged to a pressure tube and processed as above. After 16 hr at 130–132° the light yellow liquid (18.3 g) was distilled to give **20**, bp 89–90° (8 mm), $n^{25}D$ 1.4065, 2.31 g, 97.3% **20** and 1.39% **22a,b** by glpc; a mixture, bp 96–105° (8 mm) and 60–55° (0.15 mm), 2.77 g; **22a,b**, bp 50° (0.12 mm), $n^{25}D$ 1.4185, 3.49 g, 3.0% **20** and 97.0% **22a,b** by glpc; a solid residue of **21**, 4.70 g; and recovered **3** and **5** in trap, 5.37 g. Glpc analysis was done using a 6 ft × 0.25 in. Apiezon N (10%)

(27) D. J. Trecker and J. P. Henry, *J. Amer. Chem. Soc.*, **85**, 3204 (1963).

column at 150°. There was a shoulder on the peak for **20**: ir 20 ν_{CH_2} 3080; ν_{CH} 2980; 2930, 2850 (d); $\nu_{C=C}$ 1640; bands at 1025, 932, 880, 735, and 725 cm^{-1}; nmr (**20**, Figure 3), δ 1.3–1.9 (4 protons, m, CH_2 of C_4, C_5), 2.1 (2 protons, q, J = 13, 6 Hz, $CH_2CH_2CH=$), 2.75 (t of d, J_{HF} = 20 Hz, CF_2CH_2CH), 4.4 (1 proton, 5 line, J = 12 and 6 Hz, CH_2CHICH_2); nmr (**21**) δ 1.8 (6 protons, t of d, J_{HF} = 20, J = 8 Hz, CF_2CH_2CHI), 4.4 [2 protons, m, $(CHI)_2$].

Reaction of 5 and 8 to Give *endo*-2-Iodo-*exo*-3-perfluorobutylnorbornane (17).—**5** (17.3 g, 0.0500 mol), **8** (4.70 g, 0.0500 mol), and ABN (0.164 g, 1.00 mmol) were processed as above and heated for 3 hr at 70.0°. Distillation gave **17**: bp 79–82° (3.5 mm), 16.7 g (76%), a single peak by glpc; ir (KBr plates) δ_{CH} 1480, 1460, 1355, 1320; ν_{CF} 1250–1200, 1130; bands at 1030, 1020, 1010, 970, 945, 925, 910, 875, 855, 790, 760, 740, 735, 685, and 650 cm^{-1}; nmr was identical with the published spectrum of perfluoropropyl homolog.[10]

Anal. Calcd for $C_{11}H_{10}F_9I$: C, 30.02; H, 2.29; I, 28.84. Found: C, 30.2; H, 2.10; I, 28.2.

Reaction of 5 and 9 to Give 5-Perfluorobutyl-*exo*- and -*endo*-7-iodonortricyclene ($11_{a,b}$).—**5** (6.93 g, 0.0200 mol), **9** (0.921 g, 0.0100 mol), ABN (0.0328 g, 0.200 mmol), and 2-butanone (10 ml) were treated as above. After 16 hr at 70° the reaction mixture was analyzed by glpc (6-ft Apiezon N column, temperature-programmed 7°/min from 110° to 180°); adducts were found at 5.75 (3.19%), 9.5 (3.26%), and $11_{a,b}$ at 10.2 and 11.2 min (48.5 and 45.0% relative areas). The small amount of the first set of peaks precluded isolation. Distillation afforded $11_{a,b}$: bp 75–78° (1.5 mm), 3.56 g (81.3%); ir (KBr plates) ν_{CH} 3040, 3020, 3000, 2980, 2955; no bands at 1600–1900; δ_{CH} 1475, 1355, 1320, 1300; ν_{CF} 1250–1150; and bands at 1050, 1035, 1025, 980, 950, 910, 900, 880, 870, 820, 740, 730, 720, 700, and 650 cm^{-1}; nmr δ 1.0–2.68 (6 protons, m, ring protons), 3.2, (1 proton, t, J_{HF} = 17 Hz, CF_2CH–; δ 3.82 (0.9 proton, s, CHI), 4.25 (0.06 proton, s, CHI). That the perfluorobutyl group was exo was indicated by the absence of coupling of proton on C-5 to adjacent protons at a 90° dihedral angle.

Anal. Calcd for $C_{11}H_8F_9I$: C, 30.16; H, 1.84; F, 39.03; I, 28.97. Found: C, 30.4; H, 1.8; I, 27.7.

Competitive Addition of 5 to 6 and 3.—A 50 ml, three-necked, pear-shaped flask fitted with a nitrogen inlet, a Dry Ice filled condenser, and a liquid sampling tube extending to the bottom of the flask, was charged with materials as listed in Table X. The flask was partly immersed in an oil bath kept at 70° and at intervals indicated in Table X, a sample (approximately 0.010 g) was removed by suction through the sample tube. The liquid in the sample tube below the "Teflon-Varibor" valve was flushed back into the reaction by external nitrogen. Samples thus obtained from three different experiments were kept in a refrigerator and analyzed by glpc as described below.

A mixture of reaction products was weighed and weight/area factors were determined from replicate analysis as indicated in Table XI.[2] Results from these experiments were mainly used as guidance for more quantitative work, as given in Table VII.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—**1**, 591-93-5; **18**, 40735-20-4; **19**, 40735-21-5; **2**, 592-42-7; A (n = 2), 40735-22-6; B (n = 2), 40735-23-7; **3**, 3070-53-9; **20**, 40735-24-8; **21**, 40735-25-9; **22a** (cis), 40735-26-0; **22b** (trans), 40735-27-1; **4**, 3710-30-3; A (n = 4), 13105-45-8; B (n = 4), 40735-29-3; **5**, 423-39-2; **6**, 592-41-6; **7**, 592-76-7; **8**, 498-66-8; **9**, 121-46-0; **11a**, 40735-30-6; **11b**, 40735-31-7; **15**, 40735-32-8; **16**, 40735-33-9; **17**, 40735-34-0.

Supplementary Material Available.—Tables IV, V, VI, IX, X and XI and Figures 3 and 4 will appear immediately following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3167.

Reactions of Alkyl Phenyl Selenide with Benzoyl Peroxide

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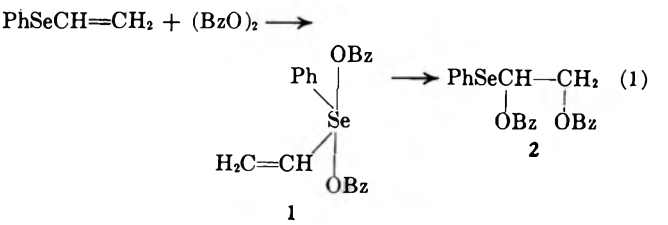
Received May 30, 1973

Benzoyl peroxide readily reacts with alkyl phenyl selenides in CCl_4 solution at room temperature to yield stable tetravalent selenium coordination compounds: alkylphenyldibenzoyloxyselenuranes (**4**). When refluxed in CCl_4, **4** decomposed into α-benzoyloxyalkyl phenyl selenides (**5**) and benzoic acid. Benzoyl peroxide further reacts with **5** to form stable selenium(IV) compounds: α-benzoyloxyalkylphenyldibenzoyloxyselenuranes (**9**). Upon heating, they decomposed into additional α-benzoyloxylation products (**10**). It is suggested that the reaction involves the initial decomposition of **4** into ion pairs and attack of the benzoate ion on the α hydrogen, producing a selenium-stabilized carbonium ion. Subsequently, the benzoyloxy moiety on the selenium rearranges the α position of the alkyl group and yields the benzoyloxylation product (**5a**).

Recently, we found that free-radical initiators such as benzoyl peroxide did not initiate the polymerization of phenylvinyl selenide. This failure was attributed to the addition of benzoyl peroxide on the selenium atom to give a tetravalent selenium(IV) compound (**1**).[1] Similar tetravalent selenium compounds have been known in the literature for some time.[2] Foster isolated diphenylselenium diacetate from the reaction of diphenylselenium oxide with acetic anhydride.[3] Stable



cyclic tetravalent selenium compounds were also prepared by the intramolecular reactions between selenium oxide and carboxylic acid.[4–6] More recently Reich

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(1) Y. Okamoto, R. Homsany, and T. Yano, *Tetrahedron Lett.*, 2531 (1972).

(2) For a discussion of bonding in high-valenced selenium compounds, see (a) J. I. Musher, *Ann. N. Y. Acad. Sci.*, 19252 (1972); (b) J. I. Musher, *Angew. Chem., Int. Ed. Engl.*, **8**, 54 (1969).

(3) D. G. Foster, *Recl. Trav. Chim. Pays-Bas*, **54**, 447 (1935).

(4) L. B. Agenas and B. Lindgren, *Acta Chem. Scand.*, **24**, 3301 (1970).

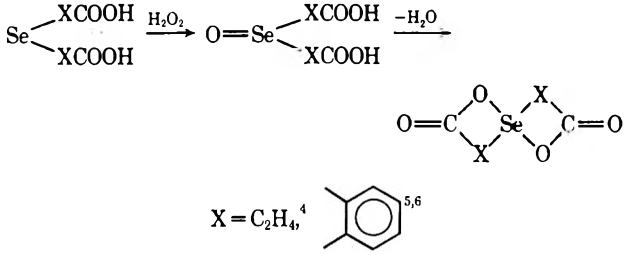
(5) R. Lesser and R. Weiss, *Ber.*, **47**, 2510 (1914).

(6) B. Lindgren, *Acta Chem. Scand.*, **26**, 2560 (1972).

TABLE I
REACTION PRODUCTS OF ALKYL PHENYL SELENIDE WITH BENZOYL PEROXIDE

Compd	Chemical shift, τ (CCl4) Alkyl protons	Aryl protons	$n^{22}D$	Bp, °C (mm)	Yield, %
CH_3SePh, **3a**	7.80 (s, 3 H)	2.50–3.00 (m, 5 H)	1.5895	70–72 (7)	
4a	7.15 (s, 3 H)	1.95–2.90 (m, 15 H)		Mp 116	92
5a	4.20 (s, 2 H)	2.10–3.05 (m, 10 H)	1.6130	120 (0.7)	60
C_2H_5SePh, **3b**	7.35 (q, 2 H) J = 7.5 Hz 8.35 (t, 3 H) J = 7.5 Hz	2.33–2.92 (m, 5 H)	1.5745	63 (3)	
4b	6.05 (q, 2 H) J = 7.5 Hz 8.22 (t, 3 H) J = 7.5 Hz	1.80–3.05 (m, 15 H)		Mp 95–99	87
5b	3.45 (q, 1 H) J = 7.0 Hz 8.30 (d, 2 H) J = 7.0 Hz	1.85–3.05 (m, 10 H)	1.5970	122 (0.3)	60
C_4H_9SePh, **3c**	7.18 (t, 2 H) J = 7.5 Hz 8.10–8.90 (m, 4 H) 9.05 (t, 3 H) J = 6.5 Hz	2.47–2.98 (m, 5 H)	1.5605	85 (3)	
4c	6.92 (t, 2 H) J = 7.5 Hz 8.10–8.90 (m, 4 H) 9.05 (t, 3 H) J = 6.5 Hz	1.80–2.98 (m, 15 H)		Mp 75–80	82
5c	3.60 (t, 1 H) J = 6.5 Hz 8.00–8.90 (m, 4 H) 9.05 (t, 3 H) J = 6.5 Hz	1.95–3.05 (m, 10 H)	1.5855	140 (0.3)	49

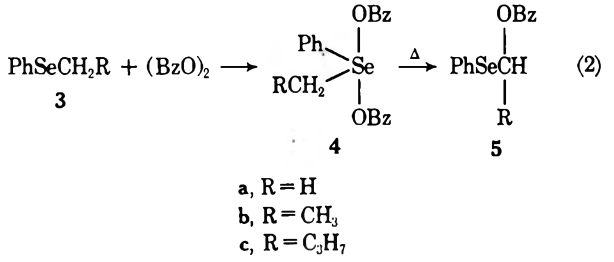
synthesized several cyclic chiral dialkoxydiaryl selenuranes.[7]



In this paper, we report the direct synthesis of the tetravalent selenium dicarboxylate by the reaction of alkyl phenyl selenides with benzoyl peroxide and the thermal decomposition products of the compounds.

Results and Discussion

In a typical reaction, a CCl_4 solution of methyl phenyl selenide (**3a**) was added dropwise to a CCl_4 solution of benzoyl peroxide. The solution was cooled using water. A slight exothermic reaction followed and a white solid precipitate was obtained. The solid was methylphenyldibenzoyloxyselenurane (yield 92%) (**4a**). **4a** was refluxed in CCl_4 for 2 hr. Upon cooling, the

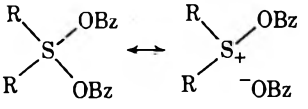


(2)

a, R = H
b, R = CH_3
c, R = C_3H_7

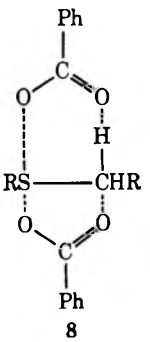
solution remained clear. It was washed with aqueous $NaHCO_3$, the CCl_4 solution was dried, and the solvent was evaporated. α-Benzoyloxymethyl phenyl selenide (**5a**) (60% yield) was obtained. From the $NaHCO_3$ extract, benzoic acid and a trace amount of phenylselenic acid were isolated. These results are summarized in Table I.

The thermal decomposition of benzoyl peroxide in the presence of alkyl ether[8,9] or sulfide[10] has been reported to yield the corresponding α-benzoyloxylation products. The reaction mechanisms were accounted for by the chain-reaction sequence. Recently, however, Pryor and Bickley reported that benzoyl peroxide decomposes at an accelerated rate in the presence of alkyl sulfide.[11] They showed that the sulfide makes a nucleophilic attack on the O–O bond of benzoyl peroxide to form an unstable intermediate which subsequently decomposes into α-benzoyloxy sulfide and benzoic acid. The intermediate was not isolated. The structure could be postulated to have a resonance hybrid of ionic (**6**) and covalent (**7**) characters.



6 **7**

Horner suggested that the possible mechanism for the formation of the α-benzoyloxylation product involves the cyclic structure **8**.[12] This structure is similar to one



8

(7) H. J. Reich, *J. Amer. Chem. Soc.*, **95**, 964 (1973). The name "selenurane" for tetrasubstituted selenium(IV) compounds was used in analogy with sulfurane.

(8) W. E. Cass, *J. Amer. Chem. Soc.*, **69**, 500 (1947).

(9) P. D. Bartlett and K. Nozaki, *J. Amer. Chem. Soc.*, **69**, 2299 (1947).

(10) H. B. Henbest, J. A. W. Reid, and C. J. M. Stirling, *J. Chem. Soc.*, 1217 (1964).

(11) S. A. Pryor and H. T. Bickley, *J. Org. Chem.*, **37**, 2855 (1972).

(12) L. Horner and E. Jurgens, *Justus Liebigs Ann. Chem.*, **602**, 135 (1957).

TABLE II

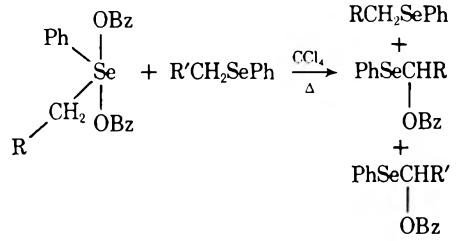
REACTION PRODUCTS OF α-BENZOYLOXYALKYL PHENYL SELENIDES WITH BENZOYL PEROXIDE

Compd	Chemical shift, τ (CCl_4) Alkyl protons	Aryl protons	Mp, °C	Yield, %
9a	3.38 (s, 2 H)	1.50–3.05 (m, 20 H)	102	85
10a	0.20 (s, 1 H)	1.80–2.70 (m, 15 H)	121–122	54
9b	8.30 (d, 3 H) J = 5.5 Hz[a]	1.20–3.00 (m, 20 H)	55	77
10b	8.25 (s, 3 H)[a]	1.70–2.60 (m, 15 H)	70–74	48

[a] The proton spectra for CH were overlapped with those of aromatic protons.

proposed by Oae and Kise to rationalize an ^{18}O exchange between a sulfoxide and acetic anhydride.[13] They suggested that the exchange involves an equilibrium between a cyclic structure similar to **8** and one like **6** ⇄ **7**. Johnson and Phillips have, however, investigated the Pummerer rearrangement of sulfonium salts.[14] Their results indicate that the initial formation of an ylide is the rate-determining step; the ylide then leads to product *via* a sulfur-stabilized carbonium ion. This mechanism is supported by Pryor and Bickley.[11]

When alkylphenyldibenzoyloxyselenuranes were decomposed in the presence of different alkyl-substituted selenides, crossover products were obtained. However, methyl phenyl selenide was found to preferentially form the α-benzoyloxylation products over ethyl and *n*-butyl phenyl selenides.

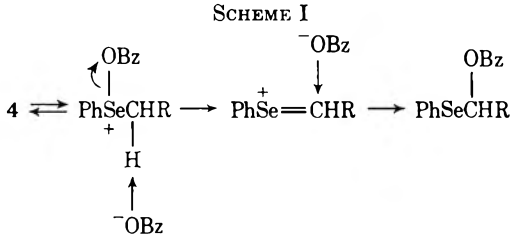


R = H, C_3H_7
R′ = H, CH_3

These results suggest that benzoate ion escapes to solution in the α-rearrangement reaction and the reaction has an intermolecular nature.

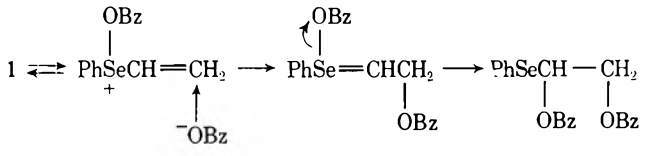
Therefore, it is likely that the reaction shown in eq 2 involves the initial formation of an ion pair and then leads to product *via* a selenium-stabilized carbonium ion as shown in Scheme I.

SCHEME I



Similarly, the reaction mechanism of eq 1 can be described as shown in Scheme II.

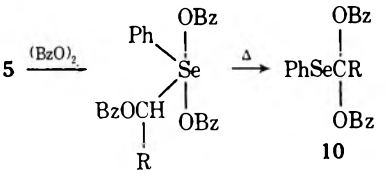
SCHEME II



(13) S. Oae and M. Kise, *Tetrahedron Lett.*, 2261 (1968).

(14) C. R. Johnson and W. G. Phillips, *J. Amer. Chem. Soc.*, **91**, 682 (1969).

Benzoyl peroxide further reacts with **5a** and **5b** at room temperature to form corresponding stable selenium(IV) compounds: α-benzoyloxyalkylphenyldibenzoyloxyselenurane (**9**). After **9** was refluxed in



a, R = H
b, R = CH_3

CCl_4 and the reaction products were treated by a procedure similar to that described above, the additional α-benzoyloxylation products (**10**) were obtained. However, the compounds tend to hydrolyze during the treatment with the aqueous $NaHCO_3$ to form diphenyl diselenide and alkyl dibenzoates.[15] The typical results of these reactions are summarized in Table II.

Experimental Section

All boiling points and melting points reported are uncorrected. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 spectrometer with tetramethylsilane as an internal reference. Infrared spectra were recorded with a Perkin Elmer Infracord. Mass spectra were obtained on a Hitachi Perkin-Elmer Model RMU-60. Benzoyl peroxide was purchased from Matheson Coleman and Bell and was recrystallized from CCl_4–methyl alcohol. Elemental analyses and molecular weight determination were made by Schwartzkopf Laboratories, New York, N. Y.

Alkyl Phenyl Selenide.—Ethyl and *n*-butyl seneides were prepared by the method of Okamoto and Yano.[17] Methyl phenyl selenide was synthesized by the method previously reported in 72% yield, bp 70–72° (7 mm) [lit.[18] bp 200–201° (760 mm)].

Reactions between Alkyl Selenides (3) and Benzoyl Peroxide.—Methyl phenyl selenide (7.0 g, 0.04 mol) in 30 ml of CCl_4 was added dropwise over 20 min to a solution of benzoyl peroxide (9.5 g, 0.04 mol) in 40 ml of CCl_4. The solution was cooled using water. A slight exothermic reaction was followed by the precipitation of a white solid. The solid was identified as methylphenyldibenzoyloxyselenurane (**4a**): yield 92%; mp 116°; mol wt (benzene) 402 (calcd for $C_{21}H_{18}O_4Se$, 413); ir (CCl_4) 1680 and 1725 cm^{-1} with no absorption bands which can be attributed to benzoyl peroxide; mass spectrum *m/e* 171, 122, 105, and 77. The CCl_4 solution of **4a** was refluxed for 2 hr and washed with aqueous $NaHCO_3$. After the CCl_4 solution was dried and the

(15) The mechanisms of the decomposition have not been investigated. However, it may be speculated that the dibenzoates react with water to form diphenyl diselenide and alkyl dibenzoates.

$$PhSeCH(OBz)_2 + H_2O \rightarrow PhSeOH + CH_2(OBz)_2$$

$$2PhSeOH \rightarrow PhSeOOH + PhSeH^{16}$$

$$PhSeH + PhSeOH \rightarrow Ph_2Se_2 + H_2O$$

(16) K. W. Bagnall, "The Chemistry of Selenium, Tellurium and Polonium," Elsevier, Amsterdam, 1966, p 164.

(17) Y. Okamoto and T. Yano, *J. Organometal. Chem.*, **29**, 99 (1971).

(18) W. J. Pope and A. Neville, *J. Chem. Soc.*, **81**, 1553 (1902).

solvent was evaporated, benzoyloxymethyl phenyl selenide (**5a**) (7 g, yield 60%) was obtained: bp 120° (0.7 mm); n^{20}D 1.6130. *Anal.* Calcd for $C_{14}H_{12}O_2Se$: C, 57.70; H, 4.10; Se, 27.14. Found: C, 57.38; H, 4.10; Se, 27.15. Ir had 1720, 2982, 3022 cm^{-1}; mass spectrum *m/e* 291, 261, 122, 105, and 77. From the $NaHCO_3$ extract, benzoic acid (5.0 g) and phenylselenic acid (0.5 g) were isolated and identified. Under similar conditions, ethyl and *n*-butyl phenyl selenides were treated with benzoyl peroxide. α-Benzoyloxyethyl and butyl phenyl selenides were obtained. *Anal.* Calcd for $C_{15}H_{14}O_2Se$ (**5b**): C, 59.01; H, 4.59; Se, 25.90. Found: C, 59.25; H, 4.70; Se, 25.40. Calcd for $C_{17}H_{18}O_2Se$ (**5c**): C, 61.26; H, 5.41; Se, 23.72. Found: 61.54; H, 5.59; Se, 23.35.

Decomposition of Alkylphenyldibenzoyloxyselenuranes in the Presence of Other Alkyl Phenyl Selenides.—Alkylphenyldibenzoyloxyselenurane was prepared by the reaction of alkyl phenyl selenide with benzoyl peroxide in CCl_4. To the solution was added a different alkyl-substituted phenyl selenide. The CCl_4 solution was gradually refluxed for 2 hr. After the CCl_4 was washed with aqueous $NaHCO_3$ and then water, the CCl_4 solution was dried and the solvent was evaporated. The products were determined by nmr measurements without isolation. The results are shown in Table III.

TABLE III
DECOMPOSITION OF ALKYLPHENYLDIBENZOYLOXYSELENURANES IN THE PRESENCE OF OTHER ALKYL PHENYL SELENIDES

Reaction system		α-Benzoyloxylation product, %	
$PhSe(OBz)_2CH_2R$ +	$PhSeCH_2R'$	$PhSeCHR$ | OBz	$PhSeCHR'$ | OBz
R	R′		
H	CH_3	92	8
C_3H_7	H	5	95
C_3H_7	CH_3	40	60

Reactions between α-Benzoyloxyalkyl Phenyl Selenides (5) and Benzoyl Peroxide.—The reactions were carried out by a procedure similar to those described in the reactions between alkyl phenyl selenides and benzoyl peroxide. Benzoyloxymethyl phenyl selenide (5.8 g, 0.020 mol) was dissolved in 60 ml of CCl_4 solution of benzoyl peroxide (5.2 g, 0.022 mol). The white solid **9a** obtained was filtered and washed with CCl_4, 9.0 g (85% yield), mp 100–102°. **9a** (8.0 g, 0.015 mol) was heated in CCl_4 for 2 hr and the solution was treated with aqueous $NaHCO_3$. After CCl_4 solutions were dried and the solvent was evaporated, dibenzoyloxymethyl phenyl selenide (**10a**) was obtained, 3.3 g (0.008 mol), yield 54%, mp 121–122°. *Anal.* Calcd for $C_{21}H_{16}O_4Se$: C, 61.16; H, 3.88; Se, 19.17. Found: C, 61.59; H, 4.10; Se, 18.80. α,α′-Dibenzoyloxyethyl phenyl selenide (**10b**) was obtained (yield 48%), mp 70–74°. *Anal.* Calcd for $C_{22}H_{18}O_4Se$: C, 62.11; H, 4.23; Se, 18.60. Found: C, 62.49; H, 4.60; Se, 18.15.

Decomposition Products of α,α′-Dibenzoyloxyalkyl Phenyl Selenide (10).—After recrystallization of **10a** from $CHCl_3$, the solvent was evaporated and the residue was treated with petroleum ether (bp 30–60°). From the petroleum ether solution, diphenyl diselenide was isolated (0.41 g), mp 57°. Its spectrum was superimposed on that of the pure compound. The petroleum ether insoluble solid was recrystallized from benzene and methylene dibenzoate was obtained (0.52 g), mp 96°, (lit.[19] mp 99°). *Anal.* Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.68; mol wt, 256. Found: C, 69.87; H, 4.48; mol wt, 281 (benzene). Ethylidene dibenzoate was isolated from the reaction of **9b** → **10b**, 0.45 g, mp 69° (lit.[19] mp 70°). *Anal.* Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.02; mol wt, 270. Found: C, 71.80; H, 5.22; mol wt, 292 (benzene).

Acknowledgment.—The authors are grateful to the Selenium-Tellurium Development Association, Inc., for the generous support of part of this work.

Registry No.—**3a**, 4346-64-9; **3b**, 17774-38-8; **3c**, 28622-61-9; **4a**, 38104-61-9; **4b**, 40902-60-1; **4c**, 40872-41-1; **5a**, 40872-42-2; **5b**, 40872-43-3; **5c**, 40872-44-4; **9a**, 40872-45-5; **9b**, 40872-46-6; **10a**, 40872-47-7; **10b**, 40872-48-8; benzoyl peroxide, 94-36-0; diphenyl diselenide, 1666-13-3; methylene dibenzoate, 5342-31-4; ethylidene dibenzoate, 4991-30-4.

(19) R. J. P. Allen, E. Jones, and P. D. Ritchie, *J. Chem. Soc.*, 524 (1957).

The Reaction of Peroxides with Phosphines in the Presence of Water

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The reaction of alkyl- or arylphosphines with dialkyl peroxides or polyperoxides in solvent systems containing water leads to the formation of alcohols or glycols from the peroxides. The quantitative formation of phosphine oxides in this reaction provides a useful analytical tool and glc analytical methods are described. The model systems investigated are (1) the reaction of styrene and 1,3-octadiene polyperoxides with triphenylphosphine and (2) the reaction of di-*n*-hexyl peroxide, 1,2-dioxane, ascaridole, and di-*tert*-butyl peroxide with tri-*n*-butylphosphine. The latter two compounds do not give quantitative amounts of phosphine oxide.

The reaction of phosphines with peroxygen compounds to give phosphine oxides was first reported in 1927[1] when the reaction of benzoyl peroxide and triphenylphosphine was described. Horner and Jurgeleit,[2] however, were the first workers to report results of a comprehensive study of the reaction of phosphines with a variety of peroxides. They reported that dialkyl peroxides react very sluggishly with triphenyl- or triethylphosphine in hydrocarbon solvent to give the corresponding dialkyl ethers and phosphine oxides. Some of their data for tertiary peroxides was subsequently shown to be in error.[3] More recently, Denney, *et al.*,[4] reported the formation of ethanol, ethylene, ethyl ether, and tributylphosphine oxide from the reaction of diethyl peroxide and tri-*n*-butylphosphine in the absence of solvent.

The ready reduction of hydroperoxides to alcohols by phosphines has been used in oxidation chemistry as a tool in determining the structure of hydroperoxides. Quantitative measurements of the resultant alcohols and phosphine oxides can be used as analytical methods.[5]

We were interested in the analysis of various olefin autoxidation product mixtures which were expected to contain both peroxide and hydroperoxide groups.

(1) F. Challenger and V. K. Wilson, *J. Chem. Soc.*, 209 (1927).

(2) L. Horner and W. Jurgeleit, *Justus Liebigs Ann. Chem.*, **591**, 138 (1955).

(3) R. Hiatt in "Organic Peroxides," Vol. 3, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1972, p 24.

(4) D. B. Denney, H. M. Relles, and A. K. Tsolis, *J. Amer. Chem. Soc.*, **86**, 4487 (1964).

(5) R. Hiatt in "Organic Peroxides," Vol. 3, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1972, p 71.

Iodometric analysis of such materials in the presence of olefin and other functional groups is very unreliable owing to various interfering reactions. It was, therefore, of interest to establish the reactivity and reaction products of a number of model peroxide systems. This paper deals with the reaction of several polyperoxides and dialkyl peroxides with tri-*n*-butyl- and triphenylphosphine. We have demonstrated that this reduction in the presence of solvent systems containing water leads to the nearly exclusive formation of alcohols and phosphine oxides as products. Glc methods for the determination of the major reaction products have been developed.

Results and Discussion

Polyperoxides.—Styrene and 1,3-octadiene polyperoxides were chosen as model systems because they are representative of olefin polyperoxides in general and because they were readily available without major by-products from the oxidation of the respective olefins.

Styrene polyperoxide in styrene was prepared by the reaction of styrene with oxygen (70 psig) in the presence of AIBN at 50° as described by Miller and Mayo.[6] They have shown that these conditions lead to styrene polyperoxide containing sytrene and oxygen in nearly 1:1 ratio with only small amounts of monomeric oxidation products. Table I shows results of the analysis of styrene polyperoxide with triphenylphosphine.

TABLE I
STYRENE POLYPEROXIDE DETERMINATIONS[a]

Run no.	Styrene convn,[b] %	O_2 uptake,[c] mol × 10^2	Ph_3PO,[d] mol × 10^2	Solvent
1	8.3	3.20	3.10	Acetone
2	10.8	4.34	4.17	Acetone
3	10.8	4.34	4.34	Benzene
4	10.8	4.34	4.13	Aqueous acetone[e]
5	13.9	5.27	5.26	Acetone

[a] A 2–3-g portion of polyperoxide solution with twice the stoichiometric amount of Ph_3P (calculated from O_2 absorption) in 4 ml of solvent in a sealed Diels–Alder tube under N_2 for 12–24 hr at ambient temperature. [b] Based on 1 mol of styrene converted per mol of O_2 absorbed. [c] By weight gain. [d] Determined by glc using internal standard. [e] A 0.25-ml portion of H_2O, 4 ml of acetone.

The utility of this method for the analysis of styrene polyperoxide is apparent. The products from the polyperoxide reaction are 1-phenylethane-1,2-diol and styrene oxide, depending on conditions (Table II).

TABLE II
PRODUCTS FROM THE REACTION OF STYRENE POLYPEROXIDE WITH TRIPHENYLPHOSPHINE

		Products[a]	
Run no.	Solvent	Glycol, mol %	Epoxide, mol %
1[b]	Benzene[c]	None	58
2	Acetone (4 ml)–H_2O (0.25 ml)	88	None
3	Acetone[c]	28	55

[a] Products by glc using internal standard based on moles of styrene polyperoxide as computed from O_2 absorption; small amounts of benzaldehyde were also observed. [b] A small amount of 1-phenylethane-1,2-diol was observed early in the reaction; it, however, disappeared ultimately. [c] Reagent grade.

(6) A. A. Miller and F. R. Mayo, *J. Amer. Chem. Soc.*, **78**, 1017 (1956).

The presence or absence of water during the reduction has a major influence on product formation. It was shown that the epoxide, once formed, is not converted to glycol under the reaction conditions. The glycol and epoxide were isolated from the reaction mixtures by silica gel chromatography or distillation for comparison with authentic samples. The rate of reaction can be qualitatively followed by glc by monitoring the disappearance of the benzaldehyde peak from the thermolysis of unreacted polyperoxide in the glc injection port.

Conjugated dienes are known to react with oxygen by both 1,2 and 1,4 addition to give polyperoxides.[7] Although the polyperoxide from 1,3-octadiene has not been reported in the literature, we experienced no difficulty in its synthesis by the method used with styrene at 50°. An ir spectrum of the polyperoxide isolated by evaporation of unreacted octadiene in a stream of nitrogen showed no significant carbonyl absorption, an indication that little polyperoxide had decomposed during the synthesis. Table III shows some representative analytical data.

TABLE III
1,3-OCTADIENE POLYPEROXIDE DETERMINATIONS[a]

Run no.	1,3-Octadiene conversion, %	O_2 uptake,[b] mol × 10^2	Ph_3PO,[c] mol × 10^2	Solvent	Time, hr
1	6.3	2.04	1.46	Acetone–H_2O	20
1a	6.3	2.04	1.97	Acetone–H_2O	72
2	9.5	3.20	3.05	Acetone–H_2O	72

[a] A 2–3-g portion of polyperoxide solution with twice the stoichiometric amount of Ph_3P in 4 ml of acetone, 0.25 ml of H_2O in a sealed Diels–Alder tube under N_2 at ambient temperature. [b] By weight gain. [c] Determined by glc using internal standard.

In one semiquantitative experiment 2.00 g (1.66×10^{-3} mol of active O_2) of oxidate was treated with 3.11×10^{-3} mol of tri-*n*-butylphosphine in 6 ml of acetone and 0.25 ml of water in the presence of benzophenone as internal standard. Successive glc analyses showed that the ratio of phosphine to phosphine oxide remained constant after 12 hr, indicating that the butylphosphine is much more reactive than triphenylphosphine.

The major reduction products in this system were studied in some detail. They were shown to be 2-octene-1,4-diol (**1**), 3-octene-1,2-diol (**2**), and 1-octene-3,4-diol (**3**), by a combination of mass, ir, nmr, and C, H analyses and comparison with the same compounds produced by $NaAlH_2(OCH_2CH_2OCH_3)_2$ reduction of the polyperoxide. In addition, **2** and **3** were synthesized by reaction of 1,3-octadiene with *m*-chloroperbenzoic acid and hydrolysis of the epoxide and glycol ester. A typical product analysis (duplicate runs) is shown in Table IV. In addition to the glc peaks attributed to diols, some smaller and lower eluting peaks were also observed and are probably due to small amounts of monools present. As_2O_3 titration of a sample containing 2.04×10^{-2} mol total O_2 by weight gain gave 0.95×10^{-3} mol of active oxygen as hydroperoxide (4.6% of the total).

Dialkyl Peroxides.—Di-*n*-hexyl peroxide was pre-

(7) O. L. Magelli and C. S. Sheppard in "Organic Peroxides," Vol. 1, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1970, p 52.

TABLE IV
TRIPHENYLPHOSPHINE REDUCTION OF 1,3-OCTADIENE POLYPEROXIDE[a]

	Sample A	Sample B
Active O_2 in aliquot, mol × 10^8 [b]	1.66	1.66
Ph_3P, mol × 10^3	3.83	3.82
Products by glc, mol × 10^3		
Ph_3PO	1.61	1.54
Ph_3P + Ph_3PO	3.75	3.71
1,4-diol (1)	0.76	0.76
1,2-diol (2)	0.35	0.33
3,4-diol (3)	0.12	0.10
Total diols	1.23	1.19

[a] A 2-g solution of polyperoxide in 1,3-octadiene, 4 ml of acetone, 0.25 ml of water, 72 hr under nitrogen in a sealed Diels–Alder tube. [b] By weight gain (oxygen uptake).

TABLE V
REDUCTION OF DI-*n*-HEXYL PEROXIDE WITH TRI-*n*-BUTYLPHOSPHINE[a]

Run no.	1	2	3[b]
	Reactants, mol × 10^3		
$(n\text{-}C_6H_{13})_2O_2$	1.03	1.00	1.05
n-Bu_3P	1.90	1.94	1.89
	Solvents, ml		
Acetone	8.0		
Water	0.4		
Benzene		8.0	8.0
	Products, mol × 10^3		
n-Hexyl alcohol	2.00	1.52	0.50
n-Hexyl ether		0.08	0.49
n-Bu_3PO	1.08	1.07	0.96

[a] Reaction carried out at ambient temperature under N_2 for 7 days in a sealed bulb or Diels–Alder tube. [b] Benzene and n-Bu_3P dried over 3A molecular sieve.

pared by the known method.[8] Table V illustrates the results obtained in the reduction of di-*n*-hexyl peroxide with n-Bu_3P in acetone–water and benzene. We were surprised to find *n*-hexyl alcohol as the major product in moist benzene (run 2); using benzene and Bu_3P (dried over 3 A molecular sieve) gave the expected ether as the major product (run 3), indicating that traces of moisture can have a significant effect on the relative amounts of ether and alcohol formed even in benzene solvent.

The effect of moisture in these systems is also shown in Table VI, where it is demonstrated that the maximum amount of alcohol is formed very soon with increasing amounts of ether as the reaction progresses and the

TABLE VI
PRODUCTS OF THE REACTION OF TRI-*n*-BUTYLPHOSPHINE WITH DI-*n*-HEXYL PEROXIDE AS A FUNCTION OF TIME[a]

	Time, hr				
	0	0.5	18	91	189	266
	Reactants, mol × 10^3					
n-Hexyl peroxide	1.05					
n-Bu_3P	1.89					
n-Bu_3PO	0.19					
	Products, mol × 10^3					
n-Hexyl alcohol		0.49	0.47	0.58	0.50	0.59
n-Hexyl ether		0.17	0.18	0.39	0.49	0.59
n-Bu_3PO (corrected)		0.50	0.54	0.80	0.95	0.95
n-Bu_3P + n-Bu_3PO		1.98	1.90	2.07	2.00	1.95

[a] Conditions are identical with those of run 3, Table V.

(8) F. Welch, H. R. Williams, and H. S. Mosher, *J. Amer. Chem. Soc.*, **77**, 551 (1955).

water present is used up. Some *n*-hexyl alcohol is observed as decomposition product when *n*-hexyl peroxide is injected into the glc instrument under conditions similar to those used in the analysis. Some of the reaction products observed may have been formed in the glc instrument. The proportion of these materials would be a maximum at low reaction times.

1,2-Dioxane was prepared by the method of Criegee and Müller.[9] Reduction of this material with n-Bu_3P in benzene without added water gave about an equal mixture of tetrahydrofuran and 1,4-butanediol in 6 days at room temperature. A similar reduction except in a 95:5 acetone–water mixture for 7 days gave essentially only 1,4-butanediol. Experiments using Ph_3P instead of n-Bu_3P indicated reaction rates ~25 times slower at ambient temperature.

Di-*tert*-butyl peroxide was shown to be virtually unreactive toward n-Bu_3P at 50°. Peroxide (1×10^{-3} mol) and n-Bu_3P (1.97×10^{-3} mol) in acetone (8 ml) and water (0.4 ml) were allowed to react for 10 days at 50° in a sealed Diels–Alder tube under nitrogen. Only 0.14×10^{-3} mol of n-Bu_3PO and no *tert*-butyl alcohol or di-*tert*-butyl ether was observed.

Ascaridole was shown to react sluggishly at 50°. Ascaridole (3.92×10^{-3} mol) and n-Bu_3P (5.31×10^{-3} mol) were allowed to react in acetone (6 ml) and water (0.25 ml) for 160 hr in a sealed bulb under nitrogen at 50°. The yield of n-Bu_3PO was 85% and the yield of *p*-menthene-1,4-diol was 23% based on ascaridole. The structure of the 1,4-diol was ascertained by comparison with an authentic sample of correct melting point and spectral properties obtained by reduction of ascaridole with $NaAlH_2(OCH_2CH_2OCH_3)_2$ in benzene. The reaction was sluggish at 50°; better results were obtained at 75°. Horner and Jurgeleit[2] have reported the reduction of ascaridole to the corresponding 1,4-endo oxide by Ph_3P at 100°. However, it has been found more recently[10] that 3,4-epoxy-*p*-menth-1-ene is the product of this reduction under Horner's conditions.

Mechanism.—Careful recent kinetic studies by Hiatt, *et al.*,[11,12] on the reaction of hydroperoxides with phosphines have confirmed earlier suggestions[2] that such peroxide reductions are nucleophilic displacements rather than free-radical reactions. However, reactions of alkoxy and alkylperoxy radicals with trivalent phosphorus compounds are also well known.[13]

Pentavalent phosphorus intermediates are involved in the reactions of trialkylphosphines[4,14] and trialkyl phosphites[15] with dialkyl peroxides.

The results of this work are generally consistent with such a nucleophilic displacement mechanism.

Equation 1 illustrates the formation of the pentavalent phosphorus intermediate (I), which in the pres-

(9) R. Criegee and G. Müller, *Ber.*, **89**, 238 (1956).

(10) A. W. P. Jarvie, C. G. Moore, and D. Skelton, *J. Polym. Sci., Part A-1*, **9**, 3105 (1971).

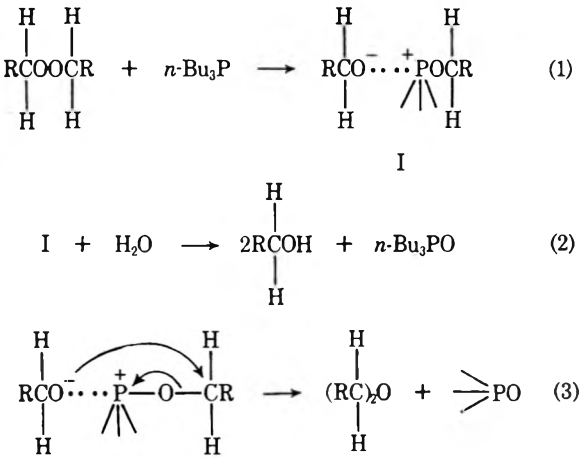
(11) R. Hiatt, R. J. Smythe, and C. McColeman, *Can. J. Chem.*, **49**, 1707 (1971).

(12) R. Hiatt and C. McColeman, *ibid.*, **49**, 1712 (1971).

(13) K. U. Ingold and B. P. Roberts, "Free Radical Substitution Reactions," Wiley-Interscience, New York, N. Y., 1971, p 118.

(14) (a) D. B. Denney and N. Gershman Adin, *Tetrahedron Lett.*, 2569 (1966); (b) D. B. Denney, *et al.*, *J. Amer. Chem. Soc.*, **91**, 5243 (1969); (c) B. C. Chang, *et al.*, *ibid.*, **93**, 4004 (1971); (d) D. B. Denney, *et al.*, *ibid.*, **94**, 245 (1972); (e) C. D. Hall, *et al.*, *ibid.*, **94**, 9264 (1972).

(15) (a) D. B. Denney and H. M. Relles, *ibid.*, **86**, 3897 (1964); (b) D. B. Denney and S. T. D. Gough, *ibid.*, **87**, 138 (1965); (c) D. B. Denney and D. H. Jones, *ibid.*, **91**, 5821 (1969).



ence of water is hydrolyzed (eq 2) to give alcohols or in an anhydrous medium (eq 3) forms ethers. The ether-forming reaction must be largely intramolecular in the case of styrene polyperoxide reacting with Ph_3P because the major product is styrene oxide. (Thermal decomposition of styrene polyperoxide gives almost exclusively benzaldehyde and formaldehyde.[16]) The apparent initial formation of alcohols in the reduction of dialkyl peroxides by tri-*n*-butylphosphine in benzene in the absence of added water could be attributed to the presence of moisture in the solvent or the phosphine, especially in view of runs 2 and 3, Table V; however, determination of the exact amount of alcohol due to the presence of moisture or due to the reaction sequence suggested by Denney, *et al.*,[4] must await further experimental clarification.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Model 137 sodium chloride spectrophotometer. Glc determinations were carried out on Perkin-Elmer Model 900 or Varian Aerograph A90P3 instruments. All melting points are corrected.

Polyperoxides.—Both styrene and 1,3-octadiene polyperoxide were prepared in an apparatus consisting of a 60 × 75 mm Pyrex thick wall bulb with a capillary neck attached to an oxygen reservoir and 100-psi test gauge with a 53 × $^1/_{16}$ in. stainless steel tube *via* a nylon ferrule and Swagelok fitting. The bulb was immersed in an Eberbach constant-temperature shaking bath using a YSI Model 74 Thermistemp temperature controller at 50°. Pressure drops were converted to volume (STP) by a calibration curve making the appropriate temperature correction for fluctuations in the oxygen reservoir temperature.

In a typical oxidation a solution of 0.0921 g of AIBN (Aldrich, twice recrystallized) in 41.7708 g of freshly distilled styrene was placed in the reactor bulb. The system was flushed twice with oxygen and then pressured to 70 psig. A pressure drop from 67.9 to 16.9 psig in 940 min corresponded to a weight gain of 1.3879 g of oxygen. Conversion of styrene was 10.8% assuming 1 mol of oxygen per mol of sytrene. Polyperoxide solutions in monomer were stored in a brown bottle at −10°.

The reduction of styrene polyperoxide by Ph_3P can be qualitatively followed by observing the disappearance of PhCHO (from polyperoxide pyrolysis) and the appearance of Ph_3PO peaks by glc as a function of time. Styrene oxide is quantitatively determined on a 5 ft × 0.25 in. 17% Carbowax 20M on AW Chromosorb P column using methyl caprate as internal standard. Styrene glycol, Ph_3P, and Ph_3PO are determined using a 1 ft × 0.25 in. 10% GE SE-30 silicone rubber on AW Chromosorb P column with benzophenone as internal standard. In analyses for Ph_3PO, the column must be preconditioned by injection of a sample containing Ph_3PO prior to the first quantitative determination. 1-Phenylethane-1,2-diol was trapped from the glc effluent and recrystallized from CCl_4, mp 64° (lit.[17] mp 67–68°), ir identical with that of authentic sample.

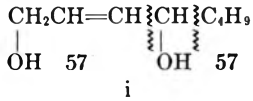
Styrene oxide was prepared from the polyperoxide as follows. Styrene polyperoxide in styrene (30 g, 0.03 mol of peroxide) was treated with Ph_3P (8.7 g, 0.033 mol) under N_2 for 5 hr at room temperature and 2 days in the refrigerator. The product was distilled and a fraction, bp 40–50° (0.5 mm), was collected; this sample was fractionated through a 2-ft microcolumn using 5 g of methyl pentadecanoate as chaser. Styrene oxide [2.1 g, 58% on polyperoxide, bp 42° (2 mm)] was collected. Both glycol and epoxide were also isolated from Ph_3P-reduced samples of polyperoxide by silica chromatography.

1,3-Octadiene polyperoxide was prepared in the apparatus described previously. A cis–trans mixture of 1,3-octadiene (from Chemical Samples Co.) was distilled and a center cut was collected. The distillate was shown to be 95+% trans by nmr and was uniform by capillary glc on a 150 ft × 10 mil squalane column at room temperature.

The reduction of 1,3-octadiene polyperoxide by Ph_3P requires ~72 hr at ambient temperature. Ph_3P and Ph_3PO were determined as before. The glycols were determined on a 5 ft × 0.25-in. Carbowax 20M (5%) on Percopak T column using benzophenone as internal standard. Response factors for the glycols were determined using the individual glycols trapped from the glc effluent.

The reduction of 1,3-octadiene polyperoxide by Ph_3P in aqueous acetone or by $NaAlH_2(OCH_2CH_2OCH_3)_2$ in benzene resulted in the same mixture of major product peaks (glc) identified as glycols. In order of elution, peak 1 was 1-octene-3,4-diol (**3**), and peaks 2 and 3 were 3-octene-1,2-diol (**2**) and 2-octene-1,4-diol (**1**), respectively. Some lower eluting peaks are presumed to be monools but were not specifically identified owing to the small amounts present. For compounds **1**, **2**, and **3** the C, H analyses were low in C owing to the presence of 3–4% water (observed by nmr).

2-Octene-1,4-diol (1) had ir 3300, 2900, 1460, 1075, 1010, 975 cm^{-1}; mass spectrum *m/e* 113 ($M - CH_2OH$)$^+$, 85 $(C_5H_9O)\cdot^+$, 69 $(HOCH{=}CHCH{=}CH)\cdot^+$, 57 (i), 31 $(CH_2OH)\cdot^+$;



i

nmr ($CDCl_3$, T60) δ 0.85 (m, 3 H, methyl), 1.4 (m, 6 H, methylene), 3.5 (s, 2 H, –OH), 4.1 (m, 3 H, methine plus methylene), 5.8 (m, 2 H, nonterminal olefinic).

3-Octene-1,2-diol (2) had ir 3300, 2900, 1450, 1065, 1025, 970, 875 cm^{-1}; mass spectrum *m/e* 144 (M^+, $C_8H_{16}O_2$), 113 ($M - CH_2OH$)$^+$, 95 (*m/e* 113 − H_2O), 69, 57; nmr ($CDCl_3$) δ 0.9 (m, 3 H, methyl), 1.4 (m, 4 H, methylene), 2.0 (m, 2 H, $CH_2CH{=}CH$), 3.6 (m, 4.1 H, OH, CH_2 next to OH), 4.2 (1 H, methine), 5.6 (m, 1.9 H, nonterminal olefin).

1-Octene-3,4-diol (3) had ir 3300, 2900, 1450, 1100, 1030, 990, 920, 830 cm^{-1}; mass spectrum *m/e* 87 $(HOCHC_4H_9)\cdot^+$, 69 (*m/e* 87 − H_2O), 58 (base peak), 57 $(CH_2{=}CHCHOH)\cdot^+$; nmr ($CDCl_3$) δ 0.9 (m, 3 H, methyl), 1.3 (5.9 H, methylene), 2.4 (2 H, –OH), 3.6 (1 H, methine adjacent to OH), 4.0 (1 H, methine), 5–6 (2.8 H, vinyl).

The 1,2 and 3,4 glycols were also synthesized from 1,3-octadiene by oxidation with *m*-chloroperbenzoic acid in $CHCl_3$ followed by hydrolysis of the epoxide and benzoate esters. The products isolated by glc trapping had the same spectral properties as the compounds obtained from the polyperoxide.

Dialkyl Peroxides.—*n*-Hexyl peroxide was prepared from *n*-hexyl methanesulfonate by the method of Mosher, *et al.*,[8] in 17% yield. The peroxide had bp 64° (0.3 mm), $n^{20}D$ 1.4244 (lit.[8] $n^{20}D$ 1.4248). Among the products of the reduction of *n*-hexyl peroxide by *n*-Bu_3P, *n*-hexyl alcohol was identified by trapping from the glc effluent and by silica gel chromatographic separation and spectral comparison with an authentic sample. *n*-Hexyl ether was separated by silica chromatography as a mixture with *n*-Bu_3P. The chromatographic results demonstrate that the products are not formed in the glc instrument. In some reduction runs using Bu_3P in acetone, aldol condensation products of acetone were also observed.

Glc analyses were carried out on a 5 ft × 0.25 in. Carbowax 20M (5%) on Percopak T column with 2-dodecanone or *n*-hexadecane as internal standards. The order of elution with increas-

(16) F. R. Mayo and A. A. Miller, *J. Amer. Chem. Soc.*, **78**, 1023 (1956).

(17) R. C. Weast, "Handbook of Chemistry and Physics," 45th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1964, p C-310.

ing temperature is *n*-hexyl alcohol, *n*-hexyl ether, *n*-Bu_3P, internal standard, and *n*-Bu_3PO.

1,2-Dioxane was prepared by the method of Criegee[9] in 18% yield. The product had bp 49° (67 mm) [lit.[9] bp 61–62° (110 mm)]; $n^{20}D$ 1.4261 (lit.[7] $n^{30}D$ 1.4262). Ir, mass, and nmr spectra confirm the structure. 1,4-Butanediol was trapped from the glc effluent of a reduced sample of 1,2-dioxane for comparison with an authentic sample.

The best column for quantitative glc analysis of the components of a reduced sample of 1,2-dioxane was a 10 ft × 0.25 in. Carbowax 20M (16.7%) on AW Chromosorb P (60–80 mesh); 2-dodecanone was used as internal standard.

Di-*tert*-butyl peroxide was obtained from Lucidol and was 99.9% pure by glc.

Ascaridole was obtained from K & K. The reduction product, *p*-menthene-1,4-diol, was prepared by hydride reduction. Ascaridole (1.7 g, 1.01×10^{-2} mol) in 30 ml of benzene was refluxed with $NaAlH_2(OCH_2CH_2OCH_3)_2$ (2.86×10^{-2} mol) for 2 hr. On cooling, 50 ml of water was added, benzene was removed on a Rotavapor, and the aqueous phase was extracted with four 300-ml portions of 1:1 ether–*n*-pentane. Removal of the solvent provided 1.8 g of residue which on two crystallizations from cyclohexane gave 1.6 g of crystals: mp 80–81° (lit.[18] mp 82°); nmr ($CDCl_3$) δ 0.8–1.0 (2 d, 6 H, methyl), 1.25 (s, 3 H, methyl), 1.5–2.0 (m, 5 H, methylene + methine), 2.3 (1 H, OH), 2.7 (1 H, OH), 5.4–5.9 (2 d, 2 H, olefinic); the OH resonance is shifted by addition of D_2O and CF_3CO_2H. The glycol as a mixture with *n*-Bu_3PO was also obtained by chromatograpic separation of a Bu_3P-reduced sample of ascaridole on basic alumina (Alcoa, pH 9).

The product mixture from *n*-Bu_3P reduction was analyzed by glc on a 5 ft × 0.25-in. Carbowax 20M (5%) on Percopak T column using methyl heptanoate as internal standard. The order of elution was internal standard, *n*-Bu_3P, ascaridole decomposition peaks, 1,4-diol, and *n*-Bu_3PO.

(18) M. Matic and D. A. Sutton, *J. Chem. Soc.*, 2679 (1952).

Acknowledgment.—We wish to thank Mr. D. L. Smith for competent laboratory assistance, the Analytical Branch for assistance with nmr, mass, and elemental analyses, and the Phillips Petroleum Company for permission to publish this work.

Registry No.—**1**, 40735-15-7; **2**, 40735-16-8; **3**, 40735-17-9; styrene polyperoxide, 27379-77-7; triphenylphosphine, 603-35-0; 1,3-octadiene polyperoxide, 40742-13-0; *n*-hexyl peroxide, 3903-89-7; tributylphosphine, 998-40-3; 1,2-dioxane, 5703-46-8; *tert*-butyl peroxide, 110-05-4; ascaridole, 512-85-6; styrene oxide, 96-09-3; *p*-menthene-1,4-diol, 40735-19-1.

Reactions of 2-Acyloxyisobutyryl Halides with Nucleosides. III.[1] Reactions of Tubercidin and Formycin

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The reaction of tubercidin with 2-acetoxyisobutyryl halides gives exclusively the 2′-*O*-acetyl-3′-halo-3′-deoxy-β-D-xylofuranosyl nucleoside (**3**) substituted at the 5′ position with a trimethyldioxolanone moiety. Treatment of **3** with methanolic ammonia rapidly removed both the acetyl and dioxolanone groups to give crystalline 4-amino-7-(3-deoxy-3-halo-β-D-xylofuranosyl)-pyrrolo[2,3-*d*]pyrimidines (**4**) which could be converted to 2′,3′-anhydrotubercidin with sodium methoxide. Catalytic hydrogenolysis of the 3′-bromo nucleoside (**4b**) gave 3′-deoxytubercidin while similar treatment of the bromo acetate (**3b**) gave both 3′-deoxytubercidin and 2′,3′-dideoxytubercidin. Similar reactions of formycin with 2-acetoxyisobutyryl bromide gave both 2′-*O*-acetyl-3′-bromo-3′-deoxy-β-D-xylofuranosyl and 3′-*O*-acetyl-2′-bromo-2′-deoxy-β-D-arabinofuranosyl nucleosides (**9** and **10**) substituted at the 5′ position as 2-acetoxyisobutyryl esters. The acetyl and acetoxyisobutyryl esters could be sequentially removed by treatment with ammonia and catalytic hydrogenolysis of the appropriate compounds gave 2′-deoxy-, 3′-deoxy-, and 2′,3′-dideoxyformycin. Treatment of **9** and **10** with sodium methoxide gave 2′,3′-anhydroformycin.

Several recent papers from this laboratory have described the reactions of 2-acetoxyisobutyryl halides (**1**) with uridine[4] and adenosine.[1] These studies, based upon earlier work by Mattocks, showed that simple cis vicinal diols react with **1** to form trans halo acetates *via* intermediate acetoxonium ions. In the case of the reaction of **1** with uridine the major products proved to be derivatives of 3′-*O*-acetyl-2′-deoxy-2′-halouridine, the unusual cis configuration of the acetyl and halo functions being explained by interaction of the C_2 carbonyl group of the uracil ring with the intermediate 2′,3′-acetoxonium intermediate.[4] On the other hand, the reaction of adenosine with **1** led predominantly to the formation of 2′-*O*-acetyl-3′-deoxy-3′-halo and 3′-*O*-acetyl-2′-deoxy-2′-halo nucleosides with the D-xylo and D-arabino configurations in a ratio of roughly 10:1.[1] These products were entirely to be expected on the assumption that the intermediate 2′,3′-acetoxonium ion was opened by halide attack without participation of the purine ring. The halo nucleosides obtained from adenosine and **1** were shown to be useful intermediates for the preparation of 3′-deoxy- and 2′,3′-dideoxyadenosine as well as of 2′,3′-anhydroadenosine.

In recent years numerous nucleoside antibiotics have been isolated from nature.[5] Analogs of adenosine have been particularly prevalent in this class and antibiotics such as 4-amino-7-(β-D-ribofuranosyl)pyrrolo-[2,3-*d*]pyrimidine (**2**, tubercidin) and 7-amino-3-(β-D-ribofuranosyl)-pyrazolo[4,3-*d*]pyrimidine (**8**, formycin) have been widely studied.[5,6] The interesting spectrum of biological activities shown by tubercidin and formycin has made the chemical modification of these molecules an attractive exercise and has led to both work on total synthesis[7] and to preparation of a variety of

(1) For part II, see A. F. Russell, S. Greenberg, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **95**, 4025 (1973).

(2) Syntex Postdoctoral Fellow, 1971–1973.

(3) Syntex Postdoctoral Fellow, 1968–1970.

(4) S. Greenberg and J. G. Moffatt, *J. Amer. Chem. Soc.* **95**, 4016 (1973).

(5) R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970.

(6) C. G. Smith, G. D. Gray, R. G. Carlson, and A. R. Hanze, *Advan. Enzyme Regul.*, **5**, 121 (1967).

(7) R. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Amer. Chem. Soc.*, **91**, 2102 (1969).

TABLE I

NMR CHEMICAL SHIFTS (PARTS PER MILLION) AT 100 MHz IN DMSO-d_6

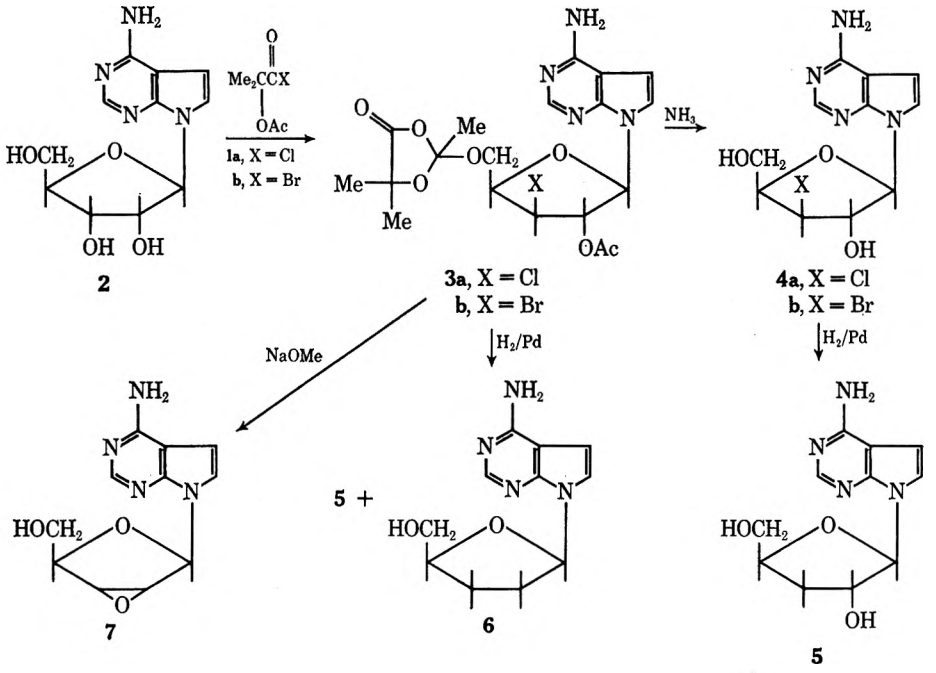
Compd	C_1′ H	C_2′ H	C_3′ H	C_4′ H	C_5′ H_a	C_5′ H_b	C_2 H[a]	C_8 H	C_6 H	Other
2	5.97 (d)	4.42 (dd)[b]	4.08 (dd)[b]	3.91 (dt)	3.59 (d)[b]		8.04 (s)	6.59 (d)	7.32 (d)	
3a free base	6.30 (d)	5.47 (dd)[c]	4.86 (m)[c]	4.50 (br dt)	3.72 (dd)	3.92 (dd)	8.06 (s)	6.66 (d)	7.25 (d)	1.44, 1.47 (s, 3, CMe_2), 1.71 (s, 3, $MeCO_3$), 2.05 (s, 3, OAc), 7.08 (s, 2, NH_2)
3b free base	6.29 (d)	5.60 (m)[c]	4.86 (m)[c]	4.38 (m)	3.76 (dd)	3.88 (dd)	8.06 (s)	6.66 (d)	7.30 (d)	1.45, 1.48 (s, 3, CMe_2), 1.72 (s, 3, $MeCO_3$), 2.06 (s, 3, OAc), 7.09 (s, 2, NH_2)
4a	6.02 (d)	4.56 (dd)[b]	4.44 (d)	4.29 (dt)	3.68 (dd)		8.04 (s)	6.60 (d)	7.26 (d)	6.23 (d, 1, C_2′ OH), 5.13 (t, 1, C_5′ OH), 7.01 (s, 2, NH_2)
4b	5.98 (d)	4.68 (ddd)	4.48 (dd)	4.18 (dt)	3.67 (dd)		8.04 (s)	6.60 (d)	7.31 (d)	6.21 (d, 1, C_2′ OH), 5.16 (t, 1, C_5′ OH), 6.99 (s, 2, NH_2)
5	6.00 (d)	4.4 (m)	1.90 (ddd) 2.16 (ddd)	4.4 (m)	3.56 (m)		8.04 (s)	6.56 (d)	7.31 (d)	5.49 (d, 1, C_2′ OH), 5.04 (t, 1, C_5′ OH), 6.95 (s, 2, NH_2)
6	6.33 (dd)	2.0–2.3 (m)	2.0–2.3 (m)	4.02 (m)	3.43 (dd)[b]	3.57 (dd)[b]	8.02 (s)	6.54 (d)	7.31 (d)	5.16 (m, 1, C_5′ OH), 6.97 (s, 2, NH_2)
7	6.28 (s)	4.28 (d)	4.17 (d)	4.11 (t)	3.55 (m)[b]		8.08 (s)	6.61 (d)	7.34 (d)	5.07 (m, 1, C_5′ OH), 7.05 (s, 2, NH_2)
8	4.94 (d)	4.47 (dd)[b]	4.09 (dd)[b]	3.96 (m)	4.6 (m)		8.13 (s)			
9[d]	5.19 (d)	6.19 (dd)	4.75 (dd)	4.4 (m)	4.21 (dd)	4.35 (dd)	8.17 (s)			1.47 (s, 6, CMe_2), 1.99 (s, 3, *t*-OAc), 2.04 (s, 3, OAc), 7.37 (s, 2, NH_2)
11a	4.89 (d)	5.21 (dd)[b]	4.49 (dd)	4.28 (m)	4.22 (dd)	4.35 (dd)	8.14 (s)			1.46 (s, 6, CMe_2), 1.96 (s, 3, *t*-OAc), 6.0 (br, 2′ OH), 7.27 (s, 2, NH_2)
11b	4.79 (d)	4.95 (dd)[b]	4.47 (dd)	4.19 (m)	3.57 (dd)	3.74 (dd)	8.14 (s)			5.85 (m, 2, OH), 7.38 (s, 2, NH_2)
12a	5.57 (d)	4.73 (dd)	4.7 (m)	3.90 (m)	4.29 (dd)	4.48 (dd)	8.15 (s)			1.46 (s, 6, CMe_2), 1.97 (s, 3, *t*-OAc), 7.29 (s, 2, NH_2)
12b	5.56 (d)	4.70 (dd)	4.58 (dd)[b]	3.73 (m)	3.73 (m)		8.07 (s)			7.78 (br s, 2, NH_2)
13a	5.01 (d)	4.70 (m)	1.95 (m) 2.30 (m)	4.37 (m)	4.13 (dd)	4.24 (dd)	8.13 (s)			1.40, 1.42 (s, 3, CMe_2), 1.95 (s, 3, *t*-OAc)
13b free base	4.91 (d)	4.58 (dt)[b]	1.88 (ddd) 2.25 (m)	4.25 (m)	3.38 (dd)[b]	3.63 (dd)[b]	8.10 (s)			7.4 (br s, 2, NH_2)
14 HCl	5.46 (dd)	2.15–2.35 (m)	4.32 (m)	3.88 (m)	3.56 (d)		8.52 (s)			9.8 (br s, 3, NH_3^+)

TABLE I
(*Continued*)

Compd	$C_{1'}$ H	$C_{2'}$ H	$C_{3'}$ H	$C_{4'}$ H	$C_{5'}$ H_a	$C_{5'}$ H_b	C_2 H[a]	C_5 H	C_6 H	Other
15	5.34 (s)	4.17 (d)	4.10 (d)	4.08 (t)	3.39 (dd)[b]	3.62 (dd)[b]	8.18 (s)			7.34 (s, 2, NH_2), 5.2 br, 1, $C_{5'}$ OH)
16 free base	5.16 (dd)	2.0–2.4 (m)	2.0–2.4 (m)	4.1 (m)	3.37 (dd)	3.61 (dd)	8.12 (s)			7.39 (s, 2, NH_2)

[a] C_2 H refers only to tubercidin derivatives and is replaced by C_5 H in the case of formycin derivatives. [b] After addition of D_2O. [c] The signals for $C_{2'}$ H and $C_{3'}$ H clearly showed slight doubling due to the chiral dioxolanone grouping. The spectrum of the hydrochloride was very similar except for the chemical shifts of C_2 H, C_5 H, and C_6 H which appeared at 8.41, 7.12 and 7.54 ppm, respectively. [d] The 2′-bromo isomer (**10**) can be recognized by its $C_{1'}$ H (5.58 ppm, d, $J_{1',2'}$ = 5 Hz), $C_{2'}$ H (4.97 ppm, dd, $J_{2',3'}$ = 4 Hz), $C_{3'}$ H (5.70 ppm, dd, $J_{3',4'}$ = 4 Hz), and 3′ OAc (2.12 ppm, s) signals.

SCHEME I



base analogs.[8] On the other hand, while 2′-deoxytubercidin has been isolated following incubation of radioactive **2** with L cells in tissue culture, little work has been done on modification of the sugar moiety of these interesting compounds.[9] In this paper we describe the reactions of tubercidin and formycin with **1** leading to syntheses of the corresponding 3′-deoxy, 2′,3′-dideoxy, and 2′,3′-anhydro analogs. The work with tubercidin has been presented previously.[10]

As an initial model, a suspension of tubercidin (**2**) in acetonitrile was treated with 2-acetoxyisobutyryl chloride (**1a**)[4] and gave a homogeneous reaction mixture after 18 hr at 37°. Following a simple work-up using either precipitation or extraction techniques a crude product was isolated in essentially quantitative yield and was shown by tlc to be predominantly a single spot with only traces of more polar by-products. The nmr spectrum of this crude product was very sharp and clearly indicated the presence of essentially a single compound identified as 4-amino-7-[2-*O*-acetyl-3-chloro-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]pyrrolo[2,3-*d*]pyrimidine (**3a**). The nature of the 5′ substituent was clear from the nmr spectrum (Table I, nonequivalent CMe_2 singlets at 1.44 and 1.47 ppm, and $MeCO_3$ at 1.71 ppm),[1,4] as was the location of the acetyl group, the $C_{2'}$ H being strongly deshielded relative to that in tubercidin. The β-D-xylo configuration of the 3′-chloro group was expected on mechanistic grounds[1,4] and was confirmed by the facile conversion of **3a** into crystalline 2′,3′-anhydrotubercidin (**7**) upon treatment with sodium methoxide (Scheme I). The nmr spectrum of **7** is very similar to those of other 2′,3′-anhydro nucleosides that we have prepared[1,11] and shows values of $J_{1',2'}$ and of $J_{3',4'} = 0$ (Table II).

Quite unlike the situations observed during reactions of adenosine,[1] guanosine,[11] and inosine[11] with **1**, it is clear from the nmr spectrum of crude **3a** that no significant formation of 3′-*O*-acetyl-2′-chloro-2′-deoxy-β-D-arabinofuranosyl nucleoside occurred. For the moment we see no explanation for the apparently complete regiospecificity shown in the tubercidin reaction. It should also be noted that **3a** should be present as a

(8) See, *e.g.*, (a) S. Watanabe, G. Matsuhashi, S. Fukatsu, G. Koyama, K. Maeda, and H. Umezawa, *J. Antibiot. Ser. A*, **19**, 93 (1966); (b) R. L. Tolman, G. L. Tolman, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **7**, 799 (1970); (c) R. A. Long, A. F. Lewis, R. K. Robins, and L. B. Townsend, *J. Chem. Soc. C*, 2443 (1971).

(9) (a) J. A. Montgomery and K. Hewson, *J. Med. Chem.*, **10**, 665 (1967); (b) M. Bobek, R. L. Whistler, and A. Block, *ibid.*, **15**, 168 (1972).

(10) A. F. Russell, S. Greenberg, and J. G. Moffatt, Abstracts of the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, CARB 14.

(11) Unpublished work by T. C. Jain, A. F. Russell, and J. G. Moffatt; see T. C. Jain and J. G. Moffatt, Abstracts of the 165th National Meeting of the American Chemical Society, Dallas, Texas, April 1973, CARB 15.

TABLE II
FIRST-ORDER COUPLING CONSTANTS (HERTZ)

Compd	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'a}$	$J_{4',5'b}$	$J_{5'a,5'b}$	$J_{5,6}$	Other
2	6	5.5	3	3	3	0	3.5	
3a	3.5	5.5	4.5	5	3.5	10	3.5	
3b	3.5	*a*	*a*	*a*	3	11	3.5	
4a	4	3	4.5	4.5	4.5	0	3.5	$J_{2',OH} = J_{5',OH} = 5$
4b	4.5	3.5	4.5	4.5	4.5	0	3.5	$J_{2',OH} = J_{5',OH} = 5$
5	2.5	3.5, 5[b]	6, 8[b]	*a*	*a*	*a*	3.5	$J_{3'a,3'b} = 13$
6	5, 5.5	*a*	*a*	4.5	4	11	3.5	
7	0	2.5	0	6	6	*a*	3.5	
8	7	5	2.5	*a*	*a*	*a*		
9	5	2	3.5	3.5	3.5	12		
11a	6	3.5	3.5	3	3	12		
11b	7	5.5	5.5	3.5	3.5	11		
12a	5.5	5.5	*a*	7	4	11		
12b	5.5	5	5	*a*	*a*	*a*		
13a	3	*a*	*a*	4	3.5	10		
13b	4.5	5, 5	7[c]	4	3	12		$J_{3'a,3'b} = 14$
14	7, 8.5	*a*	*a*	4	4	0		
15	0	2.5	0	6	6	11		
16	6, 8	*a*	*a*	3.5	3.5	11		

[a] Unresolved. [b] The relative assignments of J values are based upon analogy with the spectrum of 3′-deoxyadenosine[1] and in the present case cannot be confirmed by decoupling studies since $C_{2'}$ H and $C_{4'}$ H are very close together. [c] The $C_{3'}$ H signal is not readily subject to first-order analysis.

pair of diastereoisomers owing to the chiral nature of the dioxolanone grouping. In the adenosine and uridine series[1,4] this was always reflected in the nmr spectra by a doubling of the signals for various heterocyclic ring or sugar protons. In the case of **3a**, at least in DMSO-d_6, there is no indication whatsoever for multiple signals due to C_2 H, C_5 H, or C_6 H of the heterocyclic ring or for $C_{1'}$ H of the sugar, all of which appeared as very sharp signals. The presence of diastereomers could only be detected in the $C_{2'}$ H and $C_{3'}$ H signals, both of which appeared as closely overlapping doublets of doublets.

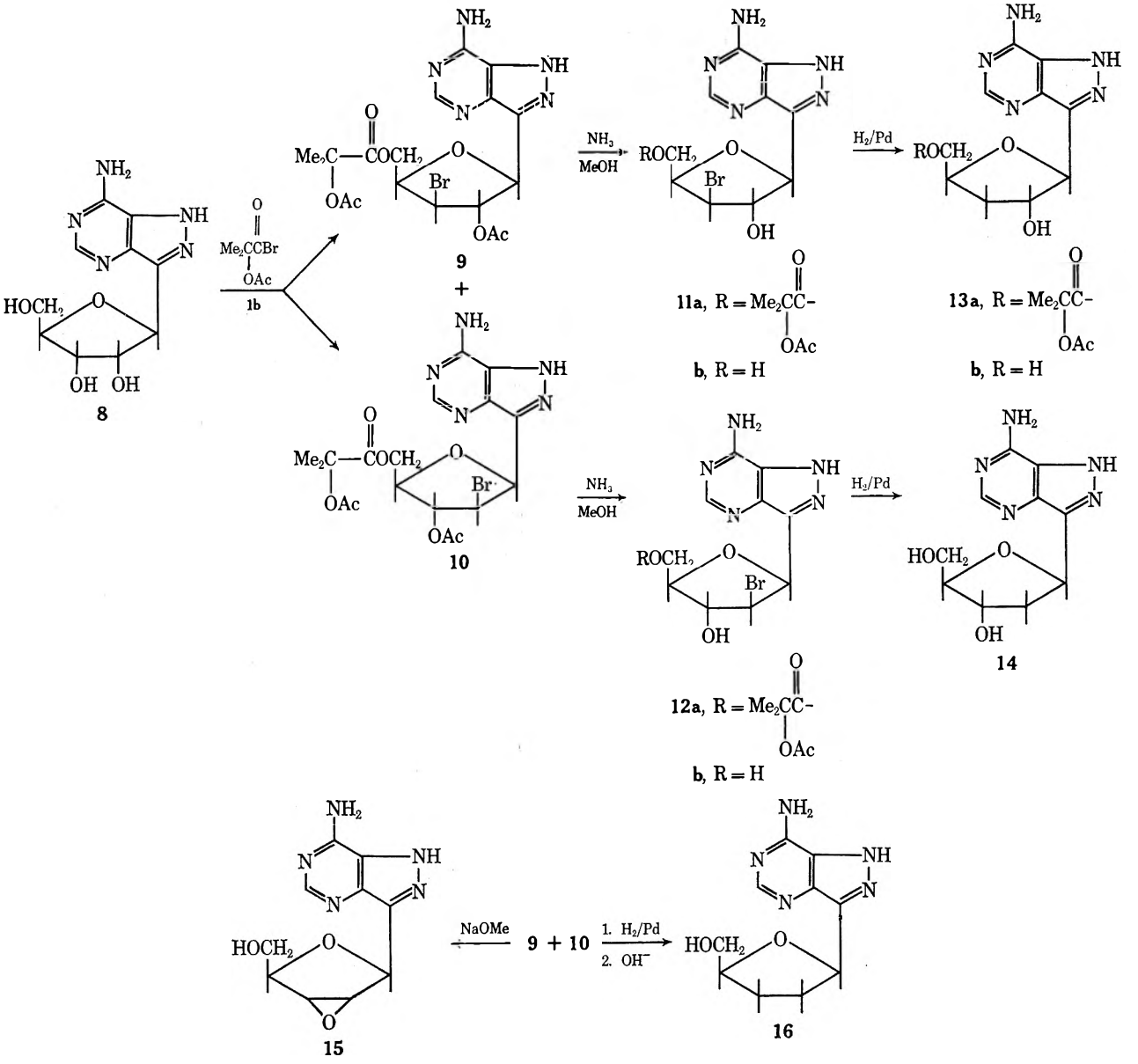
One of our principal interests was the preparation of various deoxy analogs of tubercidin and formycin *via* catalytic hydrogenolysis of the corresponding halo compounds. We have previously found that chloro compounds are generally unsuited for this purpose and accordingly studied the reaction of tubercidin with 2-acetoxyisobutyryl bromide (**1b**).[1] As in the case of the corresponding reaction with adenosine,[1] the reaction of **1b** and **2** took place within an hour at room temperature. The crude product, isolated in almost quantitative yield, was shown by tlc to consist predominantly of the 3′-bromo nucleoside (**3b**) together with only a trace amount of the comparable product from which the labile 5′-*O*-dioxolanone grouping had been lost. Once again the nmr spectrum of the crude product gave no indication of the presence of any 2′-bromo isomer and showed the 5′ position to be blocked by a dioxolanone group. As in the case of **3a**, treatment of crude **3b** with sodium methoxide at room temperature gave the epoxide in 73% yield.

In our previous studies we have made use of mild acidic hydrolysis for the stepwise removal of both dioxolanone and *O*-acetyl protecting groups. While the former were removed very rapidly by treatment with roughly 0.1 *N* methanolic hydrogen chloride, complete deacetylation under these acidic conditions took 4–8 days at room temperature. We have now observed that brief treatment of **3a** or **3b** with saturated methanolic ammonia leads to rapid cleavage of both the dioxolanone and acetyl groups giving the corresponding 4-amino-7-(3-halo-3-deoxy-β-D-xylofuranosyl)pyrrolo[2,3-*d*]pyrimidines (**4a** and **4b**) without significant epoxide formation. In this way the bromohydrin (**4b**) and the chlorohydrin (**4a**) were obtained in crystalline form in overall yields of 65 and 47% from tubercidin without any serious effort to maximize the yields through reworking the mother liquors. Catalytic hydrogenolysis of **4b** in the presence of a palladium catalyst went very smoothly and gave crystalline 3′-deoxytubercidin (**5**) in 62% yield. The structure of **5** was obvious from its nmr spectrum, the sugar portion of which was very similar to that of 3′-deoxyadenosine and showed the presence of free hydroxyl groups at both the $C_{2'}$ and $C_{5'}$ positions. In addition, the two $C_{3'}$ protons appeared as clearly separated, geminately coupled eight-line patterns at 1.90 and 2.16 ppm. Similar catalytic hydrogenolysis of the protected 3-bromo nucleoside (**3a**), followed by hydrolysis of the 3′ and 5′ substituents gave, however, two principal products that were isolated by preparative tlc and shown to be 3′-deoxytubercidin (**5**) and 2′,3′-dideoxytubercidin (**6**) in roughly equal amounts. Once again the nmr spectrum of **6** closely resembled that of 2′,3′-dideoxyadenosine and showed the 2′- and 3′-methylene groups as overlapping multiplets at 2.0–2.3 ppm.

The formation of 2′,3′-dideoxy nucleosides was previously reported in the adenosine series during hydrogenolysis of a trans bromo acetate and has been explained *via* a palladium-catalyzed trans elimination of the acetate group giving a 2′,3′ olefin which is concomitantly reduced.[1] In the absence of the 2′-*O*-acetyl group such an elimination is blocked and simple hydrogenolysis to the 3′-deoxy nucleoside is observed as above.

The reaction of formycin (**8**) with **1b** follows a puzzlingly different course. Complete reaction occurred once again at room temperature and the crude product could be isolated in quantitative yield as either the free base or the hydrobromide by use of partition or precipitation work-ups, respectively. The crude ma-

SCHEME II



terial proved to be an analytically pure but inseparable mixture of the 2′-*O*-acetyl-3′-bromo-3′-deoxy-β-D-xylofuranosyl and 3′-*O*-acetyl-2′-bromo-2′-deoxy-β-D-arabinofuranosyl nucleosides (**9** and **10**, Scheme II) in a ratio of 3:1 by nmr analysis. Unlike the results in the tubercidin series, these products showed none of the characteristics of dioxolanone groupings in either their nmr or ir spectra.[4] They were, however, clearly 5′-*O*-(2-acetoxyisobutyrate) esters, their nmr spectrum showing a *gem*-dimethyl group as a six-proton singlet at 1.47 ppm and a tertiary acetate at 1.99 ppm while the ir spectrum showed no bands near 1805 cm^{-1}. The location of the acetyl groups was readily apparent from the nmr spectrum of the mixture, and the trans stereochemistry of the bromo and acetyl functions was once again confirmed by conversion in 46% yield of the mixture to crystalline 2′,3′-anhydroformycin (**15**) upon treatment with sodium methoxide.

Brief treatment of the mixture of **9** and **10** quite selectively removed the acetyl groups while having little effect upon the acetoxyisobutyrates. The resulting isomeric trans bromohydrins (**11a** and **12a**) could be cleanly separated by preparative tlc giving the pure 3′-bromo-D-xylo (**11a**) and 2′-bromo-D-arabino (**12a**) isomers in yields of 61 and 26%, respectively, together with only 9% bromo diols (**11b** and **12b**) resulting from hydrolysis of the 5′ substituent. While we have not actually done the experiment, the very low solubility of the 2′-bromo compound (**12a**) in ethyl acetate suggests that this compound could be directly isolated from the mixture by crystallization. Complete removal of the acetoxyisobutyrate ester from **11a** and **12a** requires treatment with saturated methanolic ammonia for 48 hr at room temperature and even under these conditions is accompanied by relatively little (8%) formation of the epoxide **15**. The isomeric bromo diols (**11b** and **12b**) were readily separated by preparative tlc giving the pure isomers in yields of 57 and 18%, respectively, together with 8% of crystalline **15**, identical with that described above.

As in the tubercidin series, palladium-catalyzed hydrogenolysis of the trans bromohydrin **11b** gave 5′-*O*-(2-acetoxyisobutyryl)-3′-deoxyformycin (**13a**) in 65% yield and subsequent hydrolysis with methanolic ammonia converted this to 3′-deoxyformycin (**13b**). Similar hydrogenolysis of the bromo diol (**11b**) directly

gave analytically and spectroscopically pure **13b** both as the amorphous free base and the crystalline hydrochloride. In a similar way direct hydrogenolysis of the 2′-bromo diol (**12b**) gave 2′-deoxyformycin (**14**) which was isolated as its crystalline hydrochloride. The isomeric deoxyformycins (**13b**, **14**) could be distinguished from one another by tlc using several developments with chloroform–methanol (85:15). As expected, hydrogenolysis of the pure 5′-protected 2′-bromo nucleoside (**12a**), followed by hydrolysis with methanolic ammonia, also gave **14** uncontaminated by its 3′-deoxy isomer. Also, in agreement with what has been previously shown in the adenosine and tubercidin series, direct hydrogenolysis of the mixture of fully blocked bromo acetates (**9** and **10**), followed by removal of the 5′-substituent and preparative tlc, gave as the major product (44%) 2′,3′-dideoxyformycin (**16**). Smaller amounts of 3′-deoxyformycin (**13b**, 28%) and 2′-deoxyformycin (**14**, 3%) were also isolated and all three compounds could be obtained as their crystalline hydrochlorides. The various deoxy and dideoxy analogs of tubercidin and formycin are currently being examined for biological activities, and these results will be described elsewhere.

For the moment it is very difficult to explain the different courses followed by tubercidin and formycin in their reactions with 2-acetoxyisobutyryl halides. Thus the reaction of tubercidin leads exclusively to introduction of halogen at the 3′ position and to substitution of the 5′-hydroxyl group by a dioxolanone group. On the other hand, formycin, which is grossly very similar in structure, gives both 3′- and 2′-bromo derivatives in a ratio of roughly 3:1 and is exclusively substituted at $C_{5'}$ by an acetoxyisobutyryl ester. A possible contributing factor could be the known syn conformation of formycin at least in the crystal state[12] and in certain polynucleotides.[13] At first glance, however, one might feel that attack by halide ion from the β face at $C_{2'}$ of a 2′,3′-acetoxonium ion intermediate would be sterically inhibited if the nucleoside were preferentially in a syn conformation. Such an argument would suggest that the reaction of formycin with **1** would lead to less 2′-halogenation (**10**) than was observed with tubercidin or adenosine, a situation that is clearly not so. The reason for the clear-cut difference in the nature of the 5′ substituent is equally obscure and we are unable to provide any meaningful suggestions. A similar preference for either dioxolanone or acetoxyisobutyrate substitution at $C_{5'}$ was previously observed in the uridine series depending upon the solvent used for the reaction.[4] One possible factor that we have considered is that formycin exists as a very tenacious monohydrate that is not removed upon drying *in vacuo* at 50°. Because of this a slightly larger excess of **1b** was used and the formation of an equivalent of hydrogen bromide would be expected. The addition of 1 equiv of water to a reaction of adenosine with **1b** exactly as above does not, however, lead to any observable changes in the products. We are, accordingly, unable to provide any adequate explanation for the subtle differences observed in the reactions of tubercidin and formycin at this time.

The reactions of **1** with ribonucleosides such as tubercidin and formycin clearly provide a novel and facile route to a variety of deoxy and epoxide derivatives. These compounds are currently being examined for possible biological activities and the results of these studies will be reported elsewhere.

Experimental Section

General Methods.—The general methods used are similar to those described earlier.[4] Melting points were obtained on a hot-stage microscope and are corrected.

4-Amino-7-[2-*O*-acetyl-3-chloro-3-deoxy-5-*O*-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]pyrrolo[2,3-*d*]pyrimidine (3a).—A suspension of tubercidin (1.3 g, 4.88 mmol)[14] and **1a** (2.24 g, 13.6 mmol) in anhydrous acetonitrile was stirred at 37° for 18 hr. The resulting clear solution was evaporated *in vacuo* to a syrup that was triturated with ether giving a white precipitate that was dried *in vacuo*. This material (2.33 g, 97%) was homogeneous by tlc (chloroform–methanol, 9:1) and gave a very sharp nmr spectrum indicating the presence of a single compound shown by its elemental analysis to be the hydrochloride of **3a**: λ_{max}^{MeOH,H^+} 227 nm (ε 22,600), 271 (11,000); $\lambda_{max}^{MeOH,OH^-}$ 271 nm (ε 11,700); $[\alpha]^{23}D$ −16.9° (*c* 1.0, $CHCl_3$); ORD (MeOH) $[\Phi]_{280}^{tr}$ − 3000°, $[\Phi]_{255}$ 0°, $[\Phi]_{248}$ 1300°; ν_{max} (KBr) 1805 (dioxolanone), 1755, 1675 cm^{-1}.

For analytical purposes this material was converted with quantitative recovery into the free base by partitioning between ethyl acetate and aqueous sodium bicarbonate. The organic phase was dried and evaporated leaving a dry foam. In some experiments the free base was isolated directly (85% yield) by omitting the ether precipitation step and directly using the partitioning process.

Anal. Calcd for $C_{19}H_{23}N_4O_7Cl$ (454.86): C, 50.17; H, 5.10; N, 12.32. Found: C, 50.29; H, 5.32; N, 12.24.

4-Amino-7-[2-*O*-acetyl-3-bromo-3-deoxy-5-*O*-(2,5,5,-trimethyl-1,3-dioxolan-4-on-2-yl)-β-D-xylofuranosyl]pyrrolo[2,3-*d*]pyrimidine (3b).—A suspension of tubercidin (1.3 g, 4.88 mmol) and **1b** (3.13 g, 15 mmol) in acetonitrile (50 ml) was stirred at room temperature for 1 hr. The solvent was largely removed *in vacuo* and the residue was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic phase was washed once more with bicarbonate and then with water, dried ($MgSO_4$), and evaporated leaving crude **3b** as a white froth in quantitative yield. As obtained, this material showed essentially one spot by tlc (chloroform–methanol, 9:1) and only traces of a more polar material lacking the dioxolanone group. The nmr spectrum of the crude product confirmed that it was essentially homogeneous and for analytical purposes an aliquot was purified by preparative tlc using the above system giving **3b** with excellent recovery as a froth that could not be crystallized: λ_{max}^{MeOH,H^+} 227 nm (ε 24,500), 271 (11,500); $\lambda_{max}^{MeOH,OH^-}$ 271 nm (ε 11,800); $[\alpha]^{23}D$ −4.7° (c 0.7, $CHCl_3$); ORD (MeOH) $[\Phi]_{280}^{tr}$ − 1950°, $[\Phi]_{264}$ 0°, $[\Phi]_{242}^{pk}$ 4100°; ν_{max} (KBr) 1808, 1755, 1635 cm^{-1}.

Anal. Calcd for $C_{19}H_{23}N_4O_7Br$ (499.32): C, 45.70; H, 4.64; N, 11.22; Br, 16.00. Found: C, 45.93; H, 4.79; N, 11.03; Br, 15.86.

In one experiment the hydrobromide of **3b** was isolated in essentially quantitative yield by the direct precipitation process described for **3a**. This material was entirely satisfactory for direct use in subsequent steps.

4-Amino-7-(3-chloro-3-deoxy-β-D-xylofuranosyl)pyrrolo[2,3-*d*]-pyrimidine (4a).—A solution of the crude hydrochloride of **3a** (1.8 g, 3.66 mmol) in saturated methanolic ammonia (100 ml) was kept at room temperature for 5 hr and then evaporated to dryness *in vacuo*. The residue was partitioned between chloroform and water, the bulk of the nucleoside material being found in the aqueous phase. The aqueous phase was freed of salts by preparative tlc using chloroform–methanol (4:1) giving 808 mg (78%) of a foam that contained a minor slower moving impurity by tlc. Crystallization from methanol gave 490 mg (47%) of pure **4a**: mp 188–189°; λ_{max}^{MeOH,H^+} 228 nm (ε 24,700), 272 (11,200); $\lambda_{max}^{MeOH,OH^-}$ 270 nm (ε 12,400); $[\alpha]^{23}D$ −37.2° (c 0.5, MeOH);

(12) G. Koyama, K. Maeda, and H. Umezawa, *Tetrahedron Lett.*, 579 (1966).

(13) (a) D. C. Ward and E. Reich, *Proc. Nat. Acad. Sci.*, **61**, 1494 (1968). (b) D. C. Ward, W. Fuller, and E. Reich, *ibid.*, **62**, 581 (1969). For a review of the data concerning the conformation of formycin, see ref 5, Chapter 9.

(14) Obtained through the kindness of Dr. A. R. Hanze of The Upjohn Co., Kalamazoo, Mich.

ORD (MeOH) $[\Phi]^{tr}_{288}$ −1600°, $[\Phi]_{260}$ 0°, $[\Phi]^{pk}_{250}$ 450°, $[\Phi]_{230}$ 0°; mass spectrum *m/e* 284, 286 (M^+), 249 (M − Cl), 163 [base (B) + CH_2O], 135 (base + 2 H), 134 (base + H).

Anal. Calcd for $C_{11}H_{13}N_4O_3Cl$ (284.70): C, 46.40; H, 4.60; N, 19.68; Cl, 12.45. Found: C, 46.48; H, 4.70; N, 19.58; Cl, 12.34.

4-Amino-7-(3-bromo-3-deoxy-β-D-xylofuranosyl)pyrrolo[2,3-*d*]pyrimidine (4b).—A solution of the crude hydrobromide salt of **3b** (1.5 g, 2.58 mmol) in saturated methanolic ammonia (150 ml) was kept at room temperature for 2 hr and then evaporated to dryness. The residue was purified by preparative tlc on three plates using four developments with chloroform–methanol (9:1). The major band was eluted and crystallized from methanol–ethyl acetate giving 554 mg (65%) of **4b**: mp 179.5–180°; λ^{MeOH,H^+}_{max} 228 nm (ε 25,300), 272 (11,400); $\lambda^{MeOH,OH^-}_{max}$ 270 nm (ε 12,300); $[\alpha]^{23}D$ −21.5° (*c* 0.65, MeOH); ORD (MeOH) $[\Phi]^{tr}_{292}$ −2200°, $[\Phi]_{270}$ 0°, $[\Phi]^{pk}_{248}$ 1700°.

Anal. Calcd for $C_{11}H_{13}N_4O_3Br$ (329.16): C, 40.14; H, 3.98; N, 17.02; Br, 24.28. Found: C, 40.28; H, 4.10; N, 16.88; Br, 24.11.

3′-Deoxytubercidin (5).—A solution of **4b** (474 mg, 1.44 mmol) in methanol (100 ml) and ethyl acetate (50 ml) containing triethylamine (0.5 ml) was vigorously stirred in an atmosphere of hydrogen in the presence of a 10% palladium-on-carbon catalyst (1.0 g) for 3 days. The mixture was filtered and the filtrate was desalted by preparative tlc using chloroform–methanol (9:1). Crystallization of the uv-absorbing material from ethyl acetate gave 224 mg (62%) of **5**: mp 178–179°; λ^{MeOH,H^+}_{max} 230 nm (ε 24,200), 273 (11,100); $\lambda^{MeOH,OH^-}_{max}$ 271 nm (ε 11,200); $[\alpha]^{23}D$ −74.6° (*c* 1.0, EtOH); ORD (MeOH) $[\Phi]^{tr}_{292}$ −2400°, $[\Phi]_{267}$ 0°, $[\Phi]^{pk}_{256}$ 600°, $[\Phi]_{240}$ 0°, $[\Phi]^{tr}_{238}$ −550°, $[\Phi]_{234}$ 0°; mass spectrum (20 eV) *m/e* 251 (M + H), 250 (M^+), 177 (BH—CH=CHOH), 163 (BHCHO), 136 (B + 2 H), 135 (B + H).

Anal. Calcd for $C_{11}H_{14}N_4O_3$ (250.25): C, 52.79; H, 5.64; N, 22.39; O, 19.18. Found: C, 52.64; H, 5.73; N, 22.27; O, 19.28.

2′,3′-Dideoxytubercidin (6).—A solution of crude **3b** (from 2.25 mmol of tubercidin) in ethyl acetate (100 ml) was stirred in an atmosphere of hydrogen in the presence of triethylamine (0.35 ml) and 10% palladium on carbon (500 mg) for 22 hr. The filtered and evaporated mixture was treated with methanolic ammonia for 6 hr and then purified first on a column of silicic acid and then by preparative tlc using two developments with chloroform–methanol (9:1). Elution of the major band gave 230 mg (40%) of 3′-deoxytubercidin (**5**) identical with that above, while elution of a somewhat less polar band gave 294 mg (56%) of **6** as a homogeneous foam that could not be obtained crystalline and tenaciously held water: λ^{MeOH,H^+}_{max} 219 nm (ε 19,100), 275 nm (ε 8400); $\lambda^{MeOH,OH^-}_{max}$ 272 nm (ε 9000); $[\alpha]^{23}D$ −20.8° (*c* 1.0, MeOH); ORD (MeOH) $[\Phi]^{tr}_{288}$ −1000°, $[\Phi]_{260}$ 0°, $[\Phi]^{pk}_{250}$ 300°, $[\Phi]^{tr}_{240}$ 100°; mass spectrum (70 eV) *m/e* 59 (base peak); mass spectrum (20 eV) *m/e* 234 (M^+), 134 (B + H, base peak).

Anal. Calcd for $C_{11}H_{14}N_4O_2 \cdot 2H_2O$ (266.25): C, 48.88; H, 6.71. Found: C, 48.91; H, 6.92.

2′,3′-Anhydrotubercidin (7). A. From the Bromohydrin (4b).—A solution of **4b** (250 mg, 0.75 mmol) in methanol (10 ml) containing 0.76 mmol of sodium methoxide was kept under nitrogen at room temperature for 3 hr. The solution was then neutralized with Dowex 50 (H^+) resin and evaporated leaving a syrup that was purified by preparative tlc using several developments with chloroform–methanol (9:1) giving a major band moving just faster than **4b**. Elution of this band and crystallization from methanol–ethyl acetate gave 106 mg (57%) of **7** which decomposed gradually at 145–176° (*cf.* 2′,3′-anhydroadenosine, which decomposes above 180° without melting[1]): $\lambda^{H^+}_{max}$ 228 nm (ε 22,700), 272 (11,200); $\lambda^{OH^-}_{max}$ 270 nm (ε 12,200); $[\alpha]^{23}D$ −42.6° (*c* 0.2, MeOH); mass spectrum (70 eV) *m/e* 248 (M^+), 221 (M − HCN), 134 (B + H, base peak), 163 (B + 30).

Anal. Calcd for $C_{11}H_{12}N_4O_3$ (248.24): C, 53.22; H, 4.86; N, 22.57. Found: C, 53.19; H, 4.99; N, 22.57.

B. From Tubercidin.—The total crude extracted product from tubercidin (266 mg, 1 mmol) and **1b** as above (600 mg) was dissolved in methanol (20 ml) containing 5 mmol of sodium methoxide and stored overnight at room temperature. The solution was then heated under reflux for 30 min, neutralized with Dowex 50 (H^+) resin, and evaporated *in vacuo*. The residue was purified by preparative tlc using chloroform–methanol (85:15) giving 180 mg (73%) of chromatographically homogeneous **7** which crystallized on standing and had an nmr spectrum identical with that of the analytical sample above.

Analogous treatment of the crude chloro nucleoside (**3a**) gave **7** in the same way.

Reaction of Formycin with 1b.—Formycin monohydrate (1.14 g, 4 mmol)[15] and **1b** (2.48 ml, 16 mmol) were stirred together in acetonitrile for 3 hr. The resulting clear solution was largely evaporated *in vacuo* and a solution of the residue in ethyl acetate was washed twice with saturated aqueous sodium bicarbonate and then with water. Evaporation of the dried ($MgSO_4$) solution left 2.10 g (100%) of a mixture of **9** and **10** (3:1 by nmr) which behaved as a single spot on tlc with chloroform–methanol (9:1) but could not be crystallized: λ^{MeOH,H^+}_{max} 235 nm (ε 8300), 297 (10,800); $\lambda^{MeOH,OH^-}_{max}$ 235 nm (ε 18,900), 305 (7600); ν_{max} 1665, 1740 cm^{-1}, no peaks near 1805 cm^{-1}.

Anal. Calcd for $C_{18}H_{22}N_5O_7Br$ (500.32): C, 43.21; H, 4.43; N, 14.00. Found: C, 43.58; H, 4.67; N, 14.28.

A similar reaction on 1.3 g of formycin but using ether precipitation rather than the partitioning work-up gave 2.9 g of the almost homogeneous hydrobromide of **9** and **10** containing a small amount of deacetylated material.

7-Amino-3-[5-*O*-(2-acetoxyisobutyryl)-3-bromo-3-deoxy-β-D-xylofuranosyl]pyrazolo[4,3-*d*]pyrimidine (11a).—A solution of the mixture of **9** and **10** above (1.0 g, 2 mmol) in saturated methanolic ammonia (10 ml) was kept at room temperature for 2.5 hr and then evaporated to dryness. The residue was applied to four preparative tlc plates and developed four times with chloroform–methanol (9:1) giving a clean separation of two major bands. Elution of the faster band gave 560 mg (61%) of **11a** as a chromatographically and spectroscopically homogeneous foam that could not be crystallized: λ^{MeOH,H^+}_{max} 236 nm (ε 8600), 298 (10,100); $\lambda^{MeOH,OH^-}_{max}$ 235 nm (ε 16,800), 304 (10,000); $[\alpha]^{23}D$ 7.1° (*c* 1.0, MeOH); ORD (MeOH) $[\Phi]^{tr}_{318}$ −1400°, $[\Phi]_{302}$ 0°, $[\Phi]^{pk}_{276}$ 1850°, $[\Phi]^{tr}_{260}$ 1450°, $[\Phi]^{pk}_{236}$ 4100°; ν_{max} (KBr) 1735, 1645 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}N_5O_6Br$ (458.27): C, 41.93; H, 4.40; N, 15.28; Br, 17.44. Found: C, 41.69; H, 4.82; N, 15.13; Br, 17.78.

A sample of this material was converted into its hydrochloride, which was precipitated from methanol with ether giving a dry white powder.

Anal. Calcd for $C_{16}H_{20}N_5O_6Br \cdot HCl$ (480.73): C, 39.97; H, 4.40; N, 11.65; Br, 16.62. Found: C, 39.82; H, 4.55; N, 11.88; Br, 16.37.

7-Amino-3-[5-*O*-(2-acetoxyisobutyryl)-2-bromo-2-deoxy-β-D-arabinofuranosyl]pyrazolo[4,3-*d*]pyrimidine (12a).—Elution of the slower band from the above ammonia-treated product gave 240 mg (26%) of homogeneous **12a** which was crystallized from ethyl acetate giving 200 mg with mp 200–205° dec from ethyl acetate: λ^{MeOH,H^+}_{max} 237 nm (ε 8500), 298 (11,400); $\lambda^{MeOH,OH^-}_{max}$ 236 nm (ε 17,800), 306 (7100); $[\alpha]^{23}D$ 37.4° (*c* 1.0, MeOH); ORD (MeOH) $[\Phi]^{tr}_{320}$ −1000°, $[\Phi]_{308}$ 0°, $[\Phi]^{pk}_{240}$ 15,600°; ν_{max} (KBr) 1735, 1640 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}N_5O_6Br$ (458.27): C, 41.93; H, 4.40; N, 15.28; Br, 17.44. Found: C, 41.78; H, 4.53; N, 15.14, Br, 17.57.

A small amount (60 mg, 9%) of a mixture of **11b** and **12b** was also eluted from a much more polar band on the above plates. See below.

7-Amino-3-(3-bromo-3-deoxy-β-D-xylofuranosyl)pyrazolo[4,3-*d*]pyrimidine (11b).—A solution of the crude mixture of **9** and **10** (500 mg, 1 mmol) in saturated methanolic ammonia (5 ml) was kept at room temperature for 50 hr and then evaporated to dryness. The residue was chromatographed on two preparative plates using four developments with chloroform–methanol (85:15) which clearly separated two major slow bands from lesser amounts of epoxide (**15**, 20 mg, 8%, after crystallization from ethanol), **11a** (39 mg, 8%), and **12a** (17 mg, 3%, mp 199–202° from ethyl acetate). Elution of the faster band gave 190 mg (57%) of **11b** as a chromatographically homogeneous syrup that was crystallized from ethanol: mp 202–204° dec; λ^{MeOH,H^+}_{max} 238 nm (ε 8500), 298 (12,000); $\lambda^{MeOH,OH^-}_{max}$ 213 nm (ε 26,400), 236 (19,900), 305 (8100); $[\alpha]^{23}D$ 8.3° (*c* 1.0, MeOH); ORD (MeOH) $[\Phi]^{pk}_{296}$ 1700°, $[\Phi]_{258}$ 0°, $[\Phi]^{tr}_{234}$ −12,400°.

Anal. Calcd for $C_{10}H_{12}N_5O_3Br$ (330.15): C, 36.38; H, 3.66; N, 21.21; Br, 24.21. Found: C, 36.54; H, 3.61; N, 21.21; Br, 24.23.

7-Amino-3-(2-bromo-2-deoxy-β-D-arabinofuranosyl)pyrazolo-

(15) Obtained from Meiji Seika Kaisha, Ltd., Kawasaki, Japan, through the kindness of Dr. Kenji Maeda of the Institute of Microbial Chemistry, Tokyo, Japan. This material proved to be a tenacious monohydrate and was used as such.

[4,3-*d*]pyrimidine (**12b**).—Elution of the slower band from the isolation of **11b** gave 60 mg (18%) of **12b**, which was crystallized from ethanol giving 45 mg of crystals that underwent a loss of crystal structure at 165° and then slowly decomposed above 200°: λ_{max}^{MeOH,H^+} 236 nm (ε 7800), 298 (ε 10,500); $\lambda_{max}^{MeOH,OH^-}$ 236 nm (ε 18,800), 306 (7400).

Anal. Calcd for $C_{10}H_{12}N_5O_3Br$ (330.15): C, 36.38; H, 3.66. Found: C, 36.44; H, 3.99.

5′-*O*-(2-Acetoxyisobutyryl)-3′-deoxyformycin (13a).—A solution of **11a** (576 mg, 1.25 mmol) in methanol (100 ml) and ethyl acetate (50 ml) containing triethylamine (0.5 ml) was vigorously stirred in an atmosphere of hydrogen for 24 hr in the presence of a 10% palladium on carbon catalyst (1 g). The mixture was filtered and the filtrate desalted by preparative tlc using chloroform–methanol (9:1) to give 308 mg (65%) of **13a** as a homogeneous foam that could not be crystallized: λ_{max}^{MeOH,H^+} 236 nm (ε 9100), 297 (10,800); $\lambda_{max}^{MeOH,OH^-}$ 212 nm (ε 25,900), 236 (16,600), 305 (6700); $[\alpha]^{23}D$ −21.0° (*c* 0.7, MeOH); ORD (MeOH) $[\Phi]_{314}^{tr}$ −1400°, $[\Phi]_{290}$ 0°, $[\Phi]_{238}^{pk}$ 5200 °.

Anal. Calcd for $C_{16}H_{21}N_5O_6$ (379.37): C, 50.65; H, 5.58; N, 18.46. Found: C, 50.41; H, 5.57; N, 18.29.

3′-Deoxyformycin (13b). A. From **11b.**—A solution of **11b** (350 mg, 1.06 mmol) in methanol (180 ml) and ethyl acetate (90 ml) containing triethylamine (0.5 ml) was vigorously stirred in an atmosphere of hydrogen for 48 hr in the presence of a 10% palladium on carbon catalyst. The filtered and evaporated mixture was desalted by preparative tlc using chloroform–methanol (85:15) giving 154 mg (60%) of **13b** as a chromatographically homogeneous but hygroscopic white foam.

Anal. Calcd for $C_{10}H_{13}N_5O_3$ (251.24): C, 47.80; H, 5.22; N, 27.88. Found: C, 47.59; H, 5.27; N, 27.72.

Treatment of a portion of this substance with a small excess of methanolic hydrogen chloride gave the crystalline hydrochloride in quantitative yield with mp 207–209° from ethanol: λ_{max}^{MeOH,H^+} 234 nm (ε 8500), 295 (10,500); $\lambda_{max}^{MeOH,OH^-}$ 234 nm (ε 16,800), 303 (7800); $[\alpha]D$ −32.4° (*c* 0.4, H_2O); ORD (H_2O) $[\Phi]_{308}^{tr}$ −850°, $[\Phi]_{293}$ 0°, $[\Phi]_{260}^{pk}$ 2100°, $[\Phi]_{232}$ 0°, $[\Phi]_{220}^{tr}$ −4300°.

Anal. Calcd for $C_{10}H_{14}N_5O_3Cl$ (287.70): C, 41.74; H, 4.90; N, 24.34. Found: C, 41.58; H, 4.75; N, 24.49.

B. From **13a.**—A solution of **13a** (236 mg, 0.62 mmol) in saturated methanolic ammonia (100 ml) was kept at room temperature for 2 days. Preparative tlc using chloroform–methanol (85:15) showed that a trace of **13a** still remained, and elution of the major band gave 140 mg (90%) of **13b** identical with that above.

2′-Deoxyformycin (14).—A solution of **12a** (410 mg, 0.89 mmol) in methanol (100 ml) was hydrogenated as above in the presence of a palladium-on-carbon catalyst (400 mg). The mixture was then filtered and evaporated leaving a crude 2′-deoxy nucleoside that gave a single spot on tlc using chloroform–methanol (85:15). This material was dried, treated with methanolic sodium methoxide at room temperature for 3 hr, and then passed through a column of Dowex 50 (NH_4^+) resin. The eluate was concentrated and purified by preparative tlc using multiple developments with chloroform–methanol (4:1). The eluted material (140 mg, 63%) was treated with an excess of methanolic hydrogen chloride and crystallized from ethanol giving the hydrochloride of **14**: mp 194–196°; λ_{max}^{MeOH,H^+} 233 nm (ε 8900), 295 (10,700); $\lambda_{max}^{MeOH,OH^-}$ 234 nm (ε 16,500), 304 (7300); $[\alpha]^{23}D$ 20.8° (*c* 1.0, H_2O); ORD (H_2O) $[\Phi]_{320}^{tr}$ −500°, $[\Phi]_{303}$ 0°, $[\Phi]_{260}^{pk}$ 1300°, $[\Phi]_{241}$ 0°, $[\Phi]_{224}^{tr}$ −5900°.

Anal. Calcd for $C_{10}H_{14}N_5O_3Cl$ (287.70): C, 41.74; H, 4.90; N, 24.34; Cl, 12.32. Found: C, 42.00; H, 4.87; N, 24.14; Cl, 12.36.

2′,3′-Dideoxyformycin (16).—A solution of the crude product from formycin (3.45 mmol) and **1b** (as above) in methanol (100 ml) was vigorously stirred in the presence of triethylamine (0.5 ml) and a 10% palladium-on-carbon catalyst (500 mg) for 5 days. After filtration and evaporation, the residue was treated with methanolic sodium methoxide for 3 hr and then passed through a column of Dowex 50 (NH_4^+) resin. The residue was chromatographed on four preparative plates using eight developments with chloroform–methanol (85:15) which clearly separated three bands. Elution of the slowest band gave 35 mg (3%) of pure **14** which was isolated as the crystalline hydrochloride. Elution of the middle band gave 320 mg (28%) of **13b** which was isolated as its crystalline hydrochloride with mp 205–209° as above. Elution of the fastest band gave 360 mg (44%) of chromatographically and spectroscopically homogeneous **16** as a foam. This material was converted to its hydrochloride and crystallized from ethanol giving 275 mg of needles with mp 182–185°. The remaining material was precipitated with ether for other studies: λ_{max}^{MeOH,H^+} 234 nm (ε 8900), 296 (10,200); $\lambda_{max}^{MeOH,OH^-}$ 234 nm (ε 17,200), 304 (8000); $[\alpha]^{23}D$ 30.2° (c 1.0, H_2O); ORD (MeOH) $[\Phi]_{254}^{pk}$ 1800°, $[\Phi]_{239}$ 0°, $[\Phi]_{226}^{tr}$ −3600°; mass spectrum (hydrochloride, 20 and 70 eV) *m/e* 235 (M^+), 162 (B + 28, base peak).[16]

Anal. Calcd for $C_{10}H_{14}N_5O_2Cl$ (271.71): C, 44.20; H, 5.19; N, 25.77; Cl, 13.05. Found: C, 44.03; H, 5.18; N, 25.53; Cl, 13.24.

2′,3′-Anhydroformycin (15).—A solution of crude **9** and **10** (500 mg, 1 mmole) in methanol (35 ml) containing 2.7 mmol of sodium methoxide was kept at room temperature for 72 hr, at which point tlc showed the presence of a single product. The mixture was neutralized by portionwise addition of Dowex 50 (H^+) resin, filtered, and evaporated. The residue was purified by preparative tlc using chloroform–methanol (4:1) and the major uv-absorbing product was crystallized from methanol–ethyl acetate giving 115 mg (46%) of **15** which decomposed gradually above 190° without melting: λ_{max}^{MeOH,H^+} 235 nm (ε 8300), 297 (11,100); $\lambda_{max}^{MeOH,OH^-}$ 235 nm (ε 18,300), 305 (7700); $[\alpha]^{23}D$ 17.4° (*c* 0.5, MeOH); ORD (MeOH) $[\Phi]_{240}^{pk}$ 4600°, $[\Phi]_{230}$ 0°, $[\Phi]_{222}$ −8300°.

Anal. Calcd for $C_{10}H_{11}N_5O_3$ (249.23): C, 48.19; H, 4.45; N, 28.01. Found: C, 48.38; H, 4.62; N, 27.84.

Registry No.—**1a**, 40635-66-3; **1b**, 40635-67-4; **2**, 69-33-0; **3a**, 40627-07-4; **3a** HCl, 40627-08-5; **3b**, 40627-09-6; **3b** HBr, 40627-10-9; **4a**, 40627-11-0; **4b**, 40627-12-1; **5**, 40725-89-1; **6**, 40627-30-3; **7**, 40627-31-4; **8**, 6742-12-7; **9**, 40627-32-5; **10**, 40627-33-6; **11a**, 40627-34-7; **11a** HCl, 40627-35-8; **11b**, 40627-36-9; **12a**, 40627-37-0; **12b**, 40627-38-1; **13a**, 40627-39-2; **13b**, 40725-90-4; **13b** HCl, 40627-13-2; **14**, 40627-14-3; **14** HCl, 40627-15-4; **15**, 40627-16-5; **16**, 40627-17-6; **16** HCl, 40627-18-7.

(16) The mass spectra of a number of compounds in this paper will be discussed in detail elsewhere.

Highly Stereoselective Conversion of Prostaglandin A_2 to the 10,11α-Oxido Derivative Using a Remotely Placed Exogenous Directing Group

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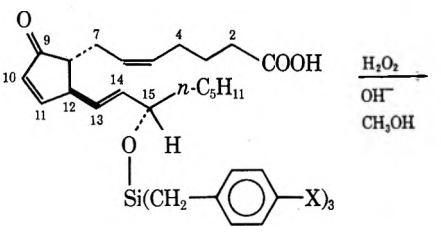
Attachment of the tri-*p*-xylylsilyl group to the 15-hydroxyl function of prostaglandin A_2 has been used to control the stereochemistry of epoxidation at the $\Delta^{10,11}$ bond using alkaline peroxide in methanol at −40°. The controller group allows formation of the 10,11α-oxide with 94% stereoselectivity. A lower degree of control (87.5% α-oxide) is observed under the same conditions using the tribenzylsilyl group as the control unit. Utilizing these exogenous controlling groups, convenient, efficient, and highly stereoselective conversion of A prostaglandins to E prostaglandins becomes possible.

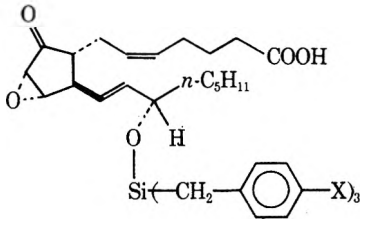
We have recently been concerned with the development of a process for stereocontrolled epoxidation of prostaglandin A_2 at the $\Delta^{10,11}$ linkage for several reasons. First, quantities of very pure 10,11α- and 10,11β-oxido derivatives were required for studies of enzymic transformations of prostaglandin A_2 in blood.[1] Additionally, two simple and stereocontrolled synthetic routes to prostaglandins have been developed lately in these laboratories[2] which lead with high efficiency to A type prostaglandins; these syntheses would become general for all primary prostaglandins with the realization of a process for stereocontrolled *10,11α-epoxidation* of the PGA's. Although our studies of the directed α-epoxidation are not yet complete, we have at this point in time succeeded in effecting epoxidation essentially quantitatively with a ratio of 10,11α-epoxide to 10,11β-epoxide (referred to herein as α/β ratio) of 94:6. Previously described epoxidations of PGA_2 derivatives,[3] including those in a very recent communication,[4] have favored only moderately the α isomer. Our plan depends on the attachment of a controller group at the 15-hydroxyl group so designed as to block the approach of a reagent to the β face of C-11 in the five-membered ring of PGA_2. In this connection it should be noted that a technique has recently been devised in this laboratory which permits highly stereoselective generation of the 15*S* configuration of the natural prostaglandins by reduction of 15-ketones bearing an appropriate controlling group at C-11.[5] Taken together, the present studies and previous work[5] illustrate the use of a controller group at C-15 to direct stereochemistry at C-11 and also the reverse, *i.e.*, the regulation of configuration at C-15 by the presence of a suitable control element at C-11.

The epoxidation of the $\Delta^{10,11}$ linkage of the A prostaglandins can be effected by the alkaline hydrogen peroxide method.[3,6,7] Two attractive candidates as



1, X = H

2, X = CH_3



3, X = H

4, X = CH_3

substrates designed to favor 10,11α-epoxidation appeared to be the 15-tribenzylsilyl ether of PGA_2 (**1**) and the 15-tri-*p*-xylylsilyl ether **2**. Figure 1 shows a view of **2** in what appears to be the energetically favorable molecular conformation.[8] The strong shielding of the β face of the cyclopentenoid unit in **2** by one of the benzenoid units of the controller is apparent. Although this shielding can be decreased to some degree by rotation about the Si–CH_2Ar bonds and/or O–Si bond, the obstruction to nucleophilic attack at the β face of C-11 remains substantial.

Reaction of prostaglandin A_2 with tribenzylsilyl chloride[9] (3.5 equiv) (prepared from benzylmagnesium chloride and silicon tetrachloride in ether, mp 140°) in dimethylformamide in the presence of 2,6-lutidine (3.5 equiv) at −20° for 24–36 hr followed by aqueous workup and chromatography of the crude product on silica gel afforded the 15-tribenzylsilyl derivative of PGA_2 (**1**) as a colorless oil, homogeneous by tlc analysis on silica gel using ether for development (R_f 0.58), and free of PGB_2 tribenzylsilyl ether (R_f 0.23), the most

(1) E. J. Corey, H. E. Ensley, L. Levine, and R. H. Abeles, in progress.

(2) (a) E. J. Corey and J. Mann and (b) E. J. Corey and G. Moinet, Symposium on Prostaglandins (Canadian Institute of Chemistry), Montreal, Canada, June 5, 1973.

(3) (a) W. P. Schneider, R. D. Hamilton, and L. E. Rhuland, *J. Amer. Chem. Soc.*, **94**, 2122 (1972); (b) G. L. Bundy, W. P. Schneider, F. H. Lincoln, and J. E. Pike, *ibid.*, **94**, 2123 (1972); (c) G. L. Bundy, E. G. Daniels, F. H. Lincoln, and J. E. Pike, *ibid.*, **94**, 2124 (1972).

(4) W. P. Schneider, G. L. Bundy, and F. H. Lincoln, *J. Chem. Soc., Chem. Commun.*, 254 (1973). Strictly quantitative measurements of α/β epoxide ratios are not available in this or previous papers.

(5) E. J. Corey, K. B. Becker, and R. K. Varma, *J. Amer. Chem. Soc.*, **94**, 8616 (1972).

(6) The epoxidation of prostaglandin A_1 using alkaline hydrogen peroxide [for method see E. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963)] was studied first in these laboratories: E. J. Corey and N. H. Anderson, unpublished results, 1968. Such direct epoxidation of the A prostaglandins is relatively nonstereoselective in protic solvents and affords a mixture of diastereomers, typically with an α/β ratio of 60:40.

(7) The epoxidation of prostaglandin A_2 methyl ester by the procedure of N. C. Yang and R. A. Finnegan, *J. Amer. Chem. Soc.*, **80**, 5845 (1958) (*tert*-butyl hydroperoxide–Triton B in aprotic medium) shows a preference opposite to the alkaline epoxidation in protic media (E. J. Corey and R. A. Ruden, unpublished experiments, 1972); for example, an α/β ratio of 25:75 is observed in benzene solution at 25°. This appears to be the method of choice at present for the preparation of 10,11β-oxido PGA's.

(8) In this conformation the two side chains are extended to avoid torsional or eclipsing interactions, and the tri-*p*-xylylsilyl group is arranged so as to minimize nonbonded intramolecular repulsions. Other conformations generated by rotation about the C-15–O bond appear to involve a major increase in steric repulsion.

(9) G. Martin and F. S. Kipping, *J. Chem. Soc.*, **95**, 302 (1909).

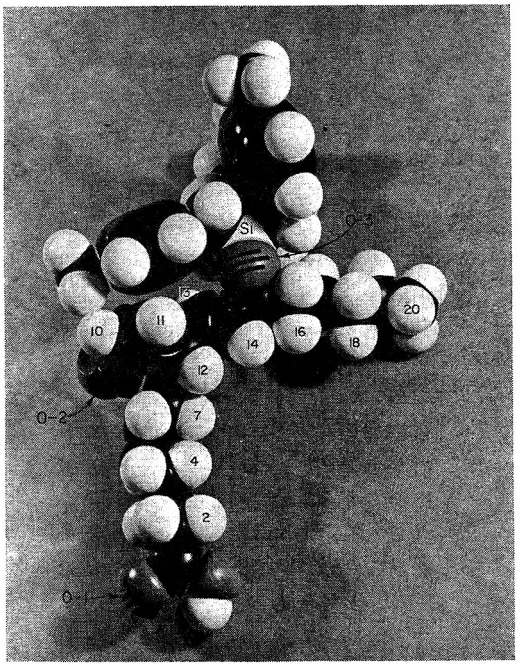


Figure 1.—CPK model of 2. Numbers on hydrogens correspond to the carbons to which they are attached. O-1 is carboxyl oxygen, O-2 carbonyl at C-9 and O-3 oxy at C-15. The lower and upper faces of the cyclopentane unit are α and β, respectively.

troublesome potential contaminant at this stage. Epoxidation of **1** was effected by reaction with a large excess of hydrogen peroxide in methanol at $-40°$ with the addition of 0.6-equiv portions of 3 *N* sodium hydroxide after 0.1, 4, 12, and 30 hr. Addition of saturated aqueous ammonium chloride, concentration at $<20°$ to remove methanol, and extraction afforded 10,11-epoxide almost quantitatively. Analysis of the product, carried out using a Waters Associates ALC-202 high-pressure liquid chromatographic unit using an ultraviolet (254 nm) detector,[10] revealed the product to be 87.5% α-oxide **3** and 12.5% of the epimer.[11] As expected, the α/β ratio was lower when the reaction was conducted at higher temperature (*e.g.*, 84.5:15.5 at $-18°$), and in addition, the epoxidation was considerably faster (*ca.* 4 hr required).

The 15-tri-*p*-xylylsilyl ether of PGA_2 (**2**)[12] upon epoxidation as described above at $-40°$ afforded 94% of the 10,11α-oxide **4** and 6% of the β-oxide. At $-20°$ epoxidation led to a product of α/β ratio of 89.5:10.5.

The epoxides **3** and **4** were converted smoothly by desilylation [acetic acid–tetrahydrofuran–water (3:1:1) 26°, 9 hr] and reduction with aluminum amalgam to prostaglandin E_2, identical in all respects with an authentic sample. Since the rate of the aluminum amalgam reduction of the 10,11α-oxide of PGA_2 is considerably faster than that of the isomeric 10,11β-oxide, it is probable that by proper choice of reaction time pure crystalline prostaglandin E_2 can be prepared efficiently from the 94:6 α,β-oxide mixture simply by use of an appropriate reaction time followed by recrystallization of the resulting PGE_2. Thus a highly stereoselective and convenient process is available for the conversion of A to E prostaglandins.[13]

These studies are continuing. It is of great interest that the replacement of hydrogen in **1** by para methyl as in **2** results in a substantial increase in the directive influence of the remote controller group. The effect is not surprising based upon the considerations outlined above; it points the way for further research.[14]

Experimental Section

15-Tri-*p*-xylylsilyloxy-PGA_2 (2).—A mixture of 201 mg (0.60 mmol) of PGA_2 (purity 70–80%) and 710 mg (1.88 mmol) of tri-*p*-xylylsilyl chloride[9,12] was dissolved in 3 ml of DMF. The slurry was cooled to $-25°$, and 80 mg (0.75 mmol) of 2,6-lutidine was added. The solution was stirred at $-25°$ for 12 hr and then another 80 mg (0.75 mmol) of 2,6-lutidine was added and the solution was stirred for another 24 hr. The solution was diluted with 15 ml of methylene chloride and extracted twice with saturated brine. After drying (Na_2SO_4) and evaporation of the solvent, the residue was chromatographed on silica gel to give 283 mg (0.42 mmol, 90–100%) of the pure 15-silyl ether of PGA_2: nmr ($CDCl_3$) δ 7.6–7.2 (multiplet, 1 H, C_{11} H), 6.9 (singlet, 12 H, ArH), 6.4–6.1 (multiplet, 1 H, C_{10} H), 5.5–5.2 (multiplet, 4 H, olefinic), 4.25–3.95 (multiplet, 1 H, C_{15} H), 3.35–0.7 (multiplet, 36 H); ir (CH_2Cl_2) 3480, 1740, 1705, 1510 cm^{-1}; mass spectrum (70 eV) *m/e* 676 (M^+).

10,11-Epoxy-15-tri-*p*-xylylsilyloxy-PGA_2 (4).—To a solution of 174.3 mg (0.26 mmol) of 15-tri-*p*-xylylsilyloxy-PGA_2 dissolved in 10 ml of methanol at $-45°$ was added 150 μl of 2 *N* NaOH and 0.5 ml (*ca.* 2 mmol) of 30% H_2O_2. The homogeneous mixture was stirred at $-45°$ for 12 hr. Another 150 μl of 2 *N* NaOH and 0.5 ml of 30% H_2O_2 were added, and the solution was stirred for 24 hr at $-45°$. The solution was added to 5 ml of saturated ammonium chloride, and the methanol was evaporated under reduced pressure. The aqueous residue was extracted twice with methylene chloride. The organic layers were washed with saturated ammonium chloride and then saturated sodium chloride solution. After drying and evaporation of the solvent, there was obtained 180 mg (102%) of the oily epoxide: nmr ($CDCl_3$) δ 6.94 (singlet, 12 H, ArH), 5.55–5.20 (multiplet, 1 H, C_{15} H), 3.67–3.51 (multiplet), 1 H, C_{10} H), 3.49–3.30 (multiplet, 1 H, C_{11} H), 3.0–0.7 (multiplet, 36 H); ir (CH_2Cl_2) 3480, 1770, 1720, 1510 cm^{-1}; mass spectrum (70 eV) *m/e* 692 (M^+).

Liquid–liquid chromatography[10] showed the mixture to consist of 94.5% α-epoxide and 5.5% β-epoxide.

10,11-Epoxy-PGA_2.—A solution of 180 mg (0.26 mmol) of 15-tri-*p*-xylylsilyloxy-PGA_2 epoxide in 12 ml of HOAc, 4 ml of H_2O, and 4 ml of THF was stirred for 6 hr at *ca.* 26°. Then the temperature was raised to 45° for 3 hr. After evaporation of the solvent there was obtained 184 mg of a mixture of trixylylsilanol and PGA_2 epoxide. The PGA_2 epoxide could not be purified by extraction into pH 8 buffer and then acidification to pH 3.5; however, it was easily purified by filtration through silica gel. Thus 87 mg of the mixture of trixylylsilanol and PGA_2 epoxide was filtered through 5 g of silica gel in ether. The silanol was eluted rapidly and then a trace of acetic acid was added to the ether. The A_2 epoxide (37 mg, 85%) was eluted rapidly: nmr ($CDCl_3$) δ 6.00–5.20 (multiplet, 6 H, olefinic, CO_2H and OH), 4.17 (broad singlet, 1 H, C_{15} H), 3.87–3.62 (multiplet, 1 H, C_{10} H), 3.55–3.38 (multiplet, 1 H, C_9 H), 3.20 (multiplet, 21 H); ir (CCl_4) 3350, 1741, 1709 cm^{-1}.

PGE_2.—To a solution of 2.75 ml of THF, 1.5 ml of H_2O, 0.1 ml of saturated sodium bicarbonate, 1 ml of ethanol, and 15 mg (0.043 mmol) of PGA_2 epoxide was added aluminum amalgam (freshly prepared from 250 mg of aluminum foil). The reaction

(10) Although the 10,11α- and 10,11β-epoxides are not cleanly separated by thin layer chromatography using a wide variety of solvent systems (*cf.* ref 3 and 4), the isomers were easily and completely resolved by the ALC-202 instrument using a 5 ft × 0.125 in. Porasil T column with 0.5% acetic acid in methylene chloride as eluent. Using a flow rate of 1 ml/min, retention times of 12 and 16 min were observed for the β- and α-epoxides, respectively. The strong ultraviolet absorbance of the controller group allowed analyses to be performed on submilligram amounts with a precision of better than 0.5%.

(11) Satisfactory infrared, nuclear magnetic resonance, and mass spectral data were obtained for all new substances reported herein.

(12) The ether **2** was prepared by the procedure used for **1** using tri-*p*-xylylsilyl chloride, mp 69°, which in turn was made by the Grignard–silicon tetrachloride method.[9]

(13) Although this development can be regarded as additional incentive to exploit the marine source of PGA_2, the soft coral *Plexaura homomalla*,[3,4] the authors urge against such exploitation as potentially damaging or disastrous to the beautiful and irreplaceable reefs of the Caribbean.

(14) This work was assisted financially by the National Institutes of Health, the National Science Foundation, and the Chas. Pfizer Co.

was allowed to proceed for 1.5 hr at 4°. The reaction mixture was centrifuged, and the aqueous THF was decanted. The alumina residue was washed twice with 10 ml of ethyl acetate containing 1% acetic acid, and the washings were combined with the THF solution. The solution was acidified with acetic acid and extracted with 10 ml of saturated sodium chloride solution. Drying (Na_2SO_4) and evaporation of the solvent gave 16.1 mg of material which was almost entirely PGE_2 with some PGA_2 and starting material (no detectable epi-PGE_2).

This was dissolved in a small amount of ethyl acetate at *ca.* 40°, and hexane was added until the solution was cloudy. The solution was cooled at −20° for 2 hr, then overnight at −75° to give 11 mg (0.031 mmol, 72.5%): mp 63–66°; nmr ($CDCl_3$, 100 MHz) δ 5.65–5.48 (multiplet, 2 H, olefinic), 5.48–5.25 (multiplet, 2 H, olefinic), 5.17 (broad singlet, 3 H, CO_2H and OH), 4.23–3.83 (multiplet, 2 H, C_{11} H and C_{15} H), 2.80–0.70 (multiplet, 23 H); ir ($CHCl_3$) 3400, 1733, 1704, 967 cm^{-1}. An additional 2 mg of PGE_2 could be obtained from the mother liquor by thin layer chromatography, raising the yield to 85%.

15-Tribenzylsilyloxy-PGA_2 (1).—A mixture of 345 mg (1.03 mmol) of PGA_2 (purity 70–80%) and 1.237 g (3.67 mmol) of tribenzylsilyl chloride was slurried under argon in 5 ml of DMF. The slurry was cooled to −20°, and 113 mg (1.03 mmol) of 2,6-lutidine in 0.5 ml of DMF was added. The solution was stirred for 12 hr at −20° and then another 101 mg (0.94 mmol) of 2,6-lutidine was added and the solution was stirred for 12 hr at −20°. After another 50 mg (0.47 mmol) of 2,6-lutidine and 12 hr at −20°, the silylation was complete. The solution was diluted with 20 ml of methylene chloride and extracted twice with 20 ml of water and then 10 ml of brine. The aqueous layers were extracted with 10 ml of methylene chloride, and the combined methylene chloride solutions were dried (Na_2SO_4). Tlc shows tribenzylsilyl chloride (R_f 0.58, Et_2O) and a small amount of 15-tribenzylsilyloxy-PGB_2 (R_f 0.23, Et_2O) as impurities. Chromatography on silica gel gave 452 mg (0.71 mmol, 88–100%) of 15-tribenzylsilyl-PGA_2 as an oil: nmr ($CDCl_3$) δ 9.8 (1 H, CO_2H), 7.40–6.80 (multiplet, 16 H, ArH and C_{11} H), 6.25–6.05 (multiplet, 1 H, C_{10} H), 5.45–5.15 (multiplet, 4 H, olefinic), 4.20–3.95 (multiplet, 1 H, C_{15} H), 3.22–2.96 (multiplet, 1 H, C_{12} H), 2.50–0.85 (multiplet, 20 H); ir (neat) 2970, 1740, 1720, 1600, 1500, 1450 cm^{-1}; mass spectrum (70 eV) *m/e* 634 (M^+), 527.

10,11-Epoxy-15-tribenzylsilyloxy-PGA_2 (3) and PGE_2.—To a solution of 64 mg (0.10 mmol) in 1 in 5 ml of methanol at −17.5° was added 1 ml (*ca.* 5 mmol) of 30% H_2O_2 followed by 20 μl (0.06 mmol) of 3 *N* NaOH.[6] After 4 hr at −17.5° another 20 μl (0.06 mmol) of 3 *N* NaOH was added and the solution was stirred for 8 hr. Another 25 μl (0.075 mmol) of 3 *N* NaOH was added, and the solution was stirred for another 18 hr. Then 2 ml of saturated NH_4Cl solution was added, and the volume was reduced to *ca.* 5 ml. The residue was diluted with 10 ml of saturated NH_4Cl solution and extracted with 10 ml of CH_2Cl_2 which was washed twice with 5 ml of saturated NH_4Cl solution and then washed with 5 ml of brine. After drying (Na_2SO_4) and evaporation of the solvent, there was obtained 60.7 mg (0.094 mmol, 94%) of a mixture of epoxides: nmr ($CDCl_3$) δ 7.32–6.80 (broad doublet, 15 H, ArH), 5.60–5.10 (multiplet, 4 H, olefinic), 4.20–3.90 (multiplet, 1 H, C_{15} H), 3.56 (doublet, J = 4 Hz, 1 H, C_{10} H), 3.35 (multiplet, 1 H, C_{11} H), 2.80–0.85 (multiplet, 27 H); ir ($CHCl_3$) 3400, 2960, 1760, 1720, 1600, 1500 cm^{-1}; mass spectrum (70 eV) *m/e* 650 (M^+), 541.

Although the two epoxides were inseparable by tlc, they were easily separated by llc.[10] This showed a mixture of 84.5:15.5 with the major isomer being the desired epoxide.

When the epoxidation was carried out at −40°, the isomer ratio was 87.5:12.5 and the yield was 95%. However, epoxidation did not occur at −78° even using 90% H_2O_2 instead of 30% H_2O_2.

The conversion of **3** to PGE_2 was carried out by the same procedure described above for the synthesis of PGE_2 from **4**.

Registry No.—1, 41366-90-9; 2, 41366-91-0; 3, 41366-92-1; PGA_2, 13345-50-1; 10,11-epoxy-PGA_2, 41366-94-3; PGE_2, 363-24-6; tri-*p*-xylylsilyl chloride, 41366-95-4; tribenzylsilyl chloride, 18740-59-5; 4, 41366-93-2.

A Study of the Scope and Mechanism of Displacement of Halogen from a Saturated Carbon by Organocadmium Reagents[1]

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Displacement of halogen with phenylcadmium reagent has been effected in several substrates: ethyl bromoacetate, ethyl α-bromopropionate, ethyl α-bromobutyrate, 3-bromocyclohexene, allyl bromide, benzyl bromide, and chloromethyl methyl ether. Under similar reaction conditions, 1-bromobutane, ethylene bromide, bromoacetaldehyde diethyl acetal, *tert*-butyl chloride, trimethylsilyl chloride, chlorocyanomethane, and 1-chloro-1-nitroethane were unreactive. With α-halo esters, an α hydrogen, as well as halogen, seems to be a minimum requirement for displacement. A carbene intermediate ($R\ddot{C}COOR'$) seems unlikely, inasmuch as none of the expected bicyclo product was found when cyclohexene was added as a carbene trapping agent. The generation of free radicals is evident from the strong esr signal observed initially on mixing of the reactants. The intermediacy of a free-radical intermediate, either by homolysis or electron transfer, is consistent with the fact that the displacement proceeds with racemization, which was established in the formation of (±)-methyl hydratropate from (*R*)-(+)-bromopropionate and phenylcadmium reagent under conditions when the starting ester was optically stable. The interesting observation has been made that the displacement in 3-bromocyclohexene proceeds without the intermediacy of free radicals, as judged by esr spectroscopy.

For some time we have been investigating a fascinating reaction of promising synthetic value, namely, the displacement of substituents—often but not always halogen—in esters, lactones, and ketones with organocadmium reagents.[2] The general reaction is represented in eq 1a and 1b.

$$\text{X}\underset{|}{\overset{|}{\text{C}}}\text{COCO}- + \text{R}_2\text{Cd} \longrightarrow \text{R}\underset{|}{\overset{|}{\text{C}}}\text{COCO}- \qquad (1a)$$

$$\text{X}\underset{|}{\overset{|}{\text{C}}}\text{CO}- + \text{R}_2\text{Cd} \longrightarrow \text{R}\underset{|}{\overset{|}{\text{C}}}\text{CO}- \qquad (1b)$$

While it had already been shown that the displacement from a phthalide[2e] was stereoselective, no such information was at hand concerning the steric course of displacement in α-halo esters[2d] when this present work was undertaken. We found that (*R*)-(+)-methyl α-bromopropionate (**1**) underwent reaction with ethereal phenylcadmium reagent to afford racemic

(1) (a) Taken in part from the Ph.D. thesis of S. J. C., University of New Hampshire, 1972. (b) Presented in part at the 164th National Meeting of the American Chemical Society, New York, N. Y., 1972, ORGN 169.

(2) (a) P. R. Jones and S. L. Congdon, *J. Amer. Chem. Soc.*, **81**, 4291 (1959); (b) P. R. Jones and A. A. Lavigne, *J. Org. Chem.*, **25**, 2020 (1960); (c) P. R. Jones, C. J. Jarboe, and R. Nadeau, *J. Organometal. Chem.*, **8**, 361 (1967); (d) P. R. Jones and J. R. Young, *J. Org. Chem.*, **33**, 1675 (1968); (e) P. R. Jones and C. J. Jarboe, *Tetrahedron Lett.*, 1849 (1969); (f) P. R. Jones and C. J. Jarboe, *J. Organometal. Chem.*, **24**, 555 (1970).

$$\underset{1}{(R)\text{-}(+)\text{-}CH_3CH(Br)CO_2CH_3} + PhCdCl \xrightarrow[\text{ether}]{60\%} \underset{2}{(\pm)\text{-}CH_3CH(Ph)CO_2CH_3} \quad (2)$$

methyl hydratropate (2) (eq 2). In the course of our investigation, we learned that Van Horn[3] had observed a similar behavior with "active" ethyl α-bromopropionate, which was converted to "racemic" ethyl α-(α-naphthyl)propionate with the α-naphthylcadmium reagent in ether–THF. Like Van Horn, we were able to show that racemization of the starting ester could not account for racemic displacement product; in addition, Van Horn carried out control experiments to demonstrate that optically active α-(α-napthyl)propionate was configurationally stable under the reaction conditions.

This racemization pathway for α-halo esters, in marked contrast to the behavior of phthalides, rules out certain mechanisms which otherwise would be attractive: an SN2 displacement, a concerted reaction involving either a four- or six-center transition state. While an SN1 reaction seemed unlikely, two mechanistic pathways warranted further experimental verification: substitution by way of a carbene (eq 3)

$$\underset{1}{CH_3CH(Br)CO_2CH_3} + PhCdCl \longrightarrow$$

$$PhH + CH_3\bar{C}(Br)CO_2CH_3, \overset{+}{C}dCl \xrightarrow{-Br^-} CH_3\ddot{C}CO_2CH_3 \xrightarrow{PhCdCl}$$

$$CH_3\bar{C}CO_2CH_3, \overset{+}{C}dCl \xrightarrow{H^+} \underset{Ph}{\underset{|}{CH_3CH}}CO_2CH_3 \quad (3)$$

$$\underset{2}{\text{Ph}}$$

and a reaction involving free radicals. Evidence against the carbene mechanism is provided by the observation that none of the expected bicyclo[4.1.0] product was formed when the reaction was carried out in the presence of cyclohexene as a carbene trapping agent. This conclusion was based on the absence of any additional peaks (aside from that of cyclohexene) in the glpc, under conditions where all the components were cleanly separated, and the lack of typical cyclopropyl protons in the nmr spectrum of the reaction mixture.

Some preliminary esr experiments provided impressive evidence for the involvement of free radicals in the displacement reaction. When reactants—phenylcadmium reagent and bromopropionate ester—were placed in a reaction flask as usual, and an aliquot immediately transferred to an esr sample tube, a strong signal was observed. As the mixture was allowed to reflux, aliquots were removed every few minutes, their esr spectra being measured as quickly as possible. After 1 hr the esr signal was weak; in 24 hr it had disappeared. In parallel experiments it could be shown by glpc analysis that the amount of hydratropic ester, the displacement product, increased up to about 1 hr and then remained unchanged for periods as long as 24 hr. No such strong initial esr signal was produced by a 0.05 *M* reaction mixture to which 0.5 g of AIBN had been added; and, indeed, no hydratropic ester was formed, as shown by glpc. It should be stressed that the strong esr signal was lacking in ethereal solutions of phenylmagnesium bromide, phenylcadmium reagent, or bromopropionate alone. An aliquot from the reaction mixture of ethereal phenylcadmium reagent and acetyl chloride, under conditions leading to acetopheneone,[4] likewise gave rise to no esr signal.

It is an attractive possibility that the displacement with bromopropionate ester may involve an electron transfer, with the intermediacy of anion radicals, a pathway postulated by Kornblum[5] for the reaction of *p*-nitrocumyl chloride with sulfur, carbon, nitrogen, and oxygen nucleophiles. As outlined in eq 4–7,

$$\underset{1}{} \xrightarrow{e} \underset{3}{[CH_3CH(Br)CO_2CH_3]\cdot^-} \longrightarrow$$

$$\underset{4}{[CH_3CHCO_2CH_3]\cdot} + Br^- \quad (4)$$

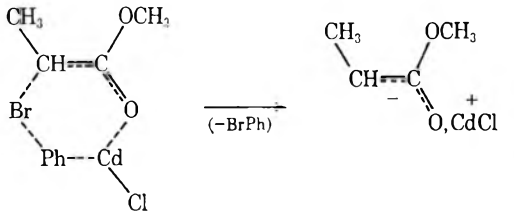
$$\underset{4}{} \xrightarrow{e} \underset{5}{[CH_3CHCO_2CH_3]^-} \quad (5)$$

$$\underset{4}{} + PhCdCl \longrightarrow \underset{6}{[CH_3CH(Ph)CO_2CH_3]\cdot^-} \quad (6)$$

$$6 + 1 \longrightarrow 2 + 3 \quad (7)$$

the bromine-containing radical anion **3** may undergo bromide elimination with generation of the radical **4**, which, in turn, can be reduced through another electron transfer to the enolate **5** or be transformed to a new radical anion **6** by addition of "phenyl anion" from the cadmium reagent. The radical anion **6**, serving itself as an electron transfer agent, would react with bromopropionate, with formation of the final product **2** and regenerated **3**.

This series of steps accounts for the observation that the generation of the "dehalogenation" product, propionate ester, is not accompanied by formation of bromobenzene, as would be required by an alternate "enolization" scheme,[6] eq 8. Bromobenzene was consistently absent from the reaction mixtures. On the contrary, bromomalonate and phenylcadmium reagent exchange, very likely by the mechanism represented in eq 8, the products formed in equal amounts being malonate and bromobenzene.[2b] Cason and Fessenden[6] had proposed the dehalogenative enolization to account for the Claisen product during interaction of ethyl α-bromoisobutyrate with butylcadmium reagent.



(8)

Although we looked for Claisen products in reactions with phenylcadmium reagents, they were never detectable by glpc, ir, or nmr.

In experiments designed to define the scope of this displacement we found that ethyl esters of α-bromoacetic, -propionic, and -butyric acids afforded the expected products with the phenylcadmium reagent, whereas none was found with α-bromoisobutyrate and ethyl α-bromisovalerate. All esters underwent some

(3) A. R. Van Horn, private communication, 1970.

(4) J. Cason, *Chem. Rev.*, **40**, 15 (1947).

(5) N. Kornblum, T. M. Davies, G. W. Earl, N. L. Holy, R. C. Kerber, M. T. Musser, and D. H. Snow, *J. Amer. Chem. Soc.*, **89**, 725 (1967).

(6) J. Cason and R. J. Fessenden, *J. Org. Chem.*, **22**, 1326 (1957).

degree of dehalogenative enolization (eq 4, 5) and the last two appeared to give coupling products, substituted succinate esters. Thus it seems that both hydrogen and halogen at the α carbon are necessary for the displacement to occur, although the steps outlined in eq 4–7 should be equally valid for α-halo esters which do not contain an α hydrogen. Reactions of ethyl- or isopropylcadmium reagents with ethyl α-bromoacetate or α-bromopropionate led to dehalogenated (enolization) ester, Claisen product, or polymeric material.

Replacement of halogen by the phenylcadmium reagent is by no means limited to esters, lactones, and ketones. We have found that allyl bromide, benzyl bromide, 3-bromocyclohexene, and chloromethyl methyl ether are all converted to their corresponding phenyl substitution products in yields of 39, 40, 81, and 34%, respectively. No attempt was made to optimize yields. Reactions proceeded readily, and glpc analysis indicated few or no side products. Unlike the reactions with esters, no strong esr signal was produced on admixture of 3-bromocyclohexene and phenylcadmium reagent, an observation which lends support for a concerted mechanism in this case. A variety of other halides failed to give any detectable amounts of displacement products: 1-bromobutane, ethylene bromide, bromoacetaldehyde diethyl acetal, *tert*-butyl chloride, trimethylsilyl chloride, chlorocyanomethane, and 1-chloro-1-nitroethane. Earlier investigators have observed the failure to effect displacement with alkylcadmium reagents at secondary,[6] tertiary,[7] and allylic[6] carbons. Our results seem to be the first instances of displacement of an allyl or benzylic halogen with a cadmium reagent, apparently by a nonradical process.

From among the displacements by organocadmium reagents with a wide variety of substrates, there must be postulated at least two distinct mechanistic pathways: a concerted, stereoselective process in the case of α'-halo lactones and a radical reaction accompanied by racemization with α-halo esters. On the basis of the preliminary esr results, the behavior of allylic halides appears to fit the former category as well, but the stereochemistry of their displacements has not yet been established.

Experimental Section

Instrumentation.—Infrared (ir) spectra were recorded as films with Perkin-Elmer Model 337 and Model 700 grating spectrophotometers. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian A-60 spectrometer and recorded in parts per million downfield from tetramethylsilane used as an internal standard. Gas–liquid phase chromatography (glpc) was accomplished with a Varian Model 90-P gas chromatograph, with a recorder speed of 2.54 cm/min and helium flow rate of 50 ml/min. The columns were all 10 ft along and 0.25 in. in diameter. Peak areas were determined from the product of the height and the width at half height. Yields were calculated from glpc by the method of peak enrichment. Esr spectra were determined with a Varian Model E-4 X-band instrument. Rotations were obtained with a Zeiss polarimeter. Melting points are corrected.

Materials.—Grignard reagents were prepared under anhydrous conditions from reagent-grade magnesium turnings and the appropriate halide. The solutions were refrigerated in serum-capped bottles, and their normality was determined by titration with *sec*-butyl alcohol as titrant and 1,10-phenanthrolene as indicator.[8] Anhydrous cadmium chloride (reagent grade) was oven dried for at least 24 hr at 110°. The halo esters were obtained from Aldrich Chemical Co., Milwaukee, Wis., unless otherwise indicated.

Apparatus.—Reactions were carried out in a flame-dried, three-necked, round-bottomed flask, fitted with a mechanical stirrer, reflux condenser, and pressure-equalizing addition funnel. Grignard reagents were transferred to the flask from the serum-capped bottles with a 20-ml syringe. Nitrogen was not used as an inert atmsophere, except where noted.

Reaction of Phenylcadmium Reagent with Ethyl α-Bromopropionate.—The following is typical of displacements carried out with ethyl α-bromoacetate, -propionate, and -butyrate.

Phenylcadmium reagent (0.10 mol) in 100 ml of anhydrous ether was prepared from the Grignard reagent (22 ml, 0.10 mol) and 18.33 g (0.10 mol) of anhydrous cadmium chloride. After a negative Gilman test,[9] 6.5 ml (0.05 mol) of ethyl α-bromopropionate in 25 ml of anhydrous ether was added dropwise to the solution, and stirring at reflux was maintained for 3 hr. The mixture was then hydrolyzed with 10 ml of water, the ether layer was dried with $MgSO_4$, and the solvent was removed in a rotary evaporator. Some of the crude material was injected into a glpc column (10% Carbowax, 150°) and the peaks were collected directly onto salt plates, from which the infrared spectra were measured. The first peak (1.1 cm), too volatile to collect, was probably ether, inasmuch as an injection of pure ether emerged at this point on the chromatogram. The next peak appeared at 1.7 cm and the ir spectrum indicated it to be ethyl propionate (as shown by comparison with Sadtler[10] Spectrum No. 303) contaminated with benzene. That benzene and ethyl propionate were emerging from the column at the same place was confirmed by their identical retention times under the same column conditions in a separate experiment. The next peak at 5.5 cm was identified as ethyl α-bromopropionate by comparison with an ir spectrum of authentic material. Ethyl hydratropate at 26.4 cm was identified in a similar way. The final peak, appearing at about 56 cm on the chromatogram, was collected as a white solid, mp 68–70° [lit.[11] mp (biphenyl) 70°].

Reaction of Ethyl α-Bromoisobutyrate with Phenylcadmium Reagent.—The following description is typical of the results with ethyl α-bromoisobutyrate and -isovalerate. The crude mixture, obtained from reaction of 9.75 g (0.05 mol) of ethyl α-bromoisobutyrate and 0.10 mol of phenylcadmium reagent for 3 hr at ice-bath, room, or reflux temperature, was analyzed on an SAIB column at 170°. In addition to peaks at 5.7 (starting bromo ester and bromobenzene), 22.0 (phenol), and 46.0 cm (biphenyl, mp 69–70°), one at 30.0 cm was collected and analyzed: ν_{CO} 1730 cm^{-1}; bp (micro) 238–240° (760 mm) [lit.[12] bp (diethyl tetramethylsuccinate) 115–121° (15 mm); 238–240° (760 mm)].

Reaction of Phenylcadmium Reagent with (*R*)-(+)-Methyl α-Bromopropionate.—(*S*)-(−)-Methyl lactate, α_{578}^{26} −9.67° (neat, *l* 1 dm), obtained by esterification of (*S*)-(+)-lactic acid with diazomethane, was converted to (*R*)-(+)-methyl α-bromopionate α_{578}^{26} +66.21° (neat, *l* 1 dm), according to the method of Gerrand and Richmond.[13] To an ethereal solution of 0.04 mol of phenylcadmium reagent was added dropwise 3.34 g (0.02 mol) of the (+)-bromo ester, and then the mixture was allowed to reflux for 3 days. It was hydrolyzed with 10 ml of distilled water, and the pasty, gray-white precipitate was washed three times with 25-ml portions of anhydrous ether; the washings were combined with the original liquid layer. The solution was dried over $MgSO_4$ and the ether was removed on the rotary evaporator. The crude reaction mixture was then separated by vacuum distillation, the fraction, bp 55–60° (1 mm), being collected [lit.[14] bp 62–65° (0.5 mm)], α_{578}^{27} +0.06° (neat, *l* 0.2 dm). The ir spectrum of this product indicated that it was methyl hydratropate, but a chromatogram, (SAIB, 170°) showed that, besides the methyl hydratropate, a small amount of biphenyl was also present.

(7) H. Gilman and J. F. Nelson, *Recl. Trav. Chim. Pays-Bas*, **55**, 518 (1936).

(8) S. C. Watson and J. F. Eastham, *J. Organometal. Chem.*, **9**, 165 (1967).

(9) H. Gilman and F. Schulze, *J. Amer. Chem. Soc.*, **47**, 2002 (1925).

(10) "The Sadtler Standard Spectra," Sadtler Research Laboratories, Philadelphia, Pa., 1965.

(11) R. C. Weast and S. M. Selby, Ed., "Handbook of Chemistry and Physics," 47th ed, The Chemical Rubber Company, Cleveland, Ohio, 1966.

(12) B. E. Hudson, Jr., and C. R. Hauser, *J. Amer. Chem. Soc.*, **63**, 3156 (1941).

(13) W. Gerrard and M. J. Richmond, *J. Chem. Soc.*, 853 (1945).

(14) S. M. McElvain and C. L. Stevens, *J. Amer. Chem. Soc.*, **69**, 2663 (1947).

The sample was further purified by preparative glpc (SAIB, 170°), α_{578}^{27} +0.02° (neat, l 0.1 dm). The amide of hydraptropic acid was prepared by saponification of methyl hydratropate and treatment of the intermediate acid chloride ($SOCl_2$) with concentrated ammonia, mp 91–92° (lit.[15] mp 91–92°).

Similar results were obtained when the reaction was repeated for a 3-hr reflux period with 0.05 mol of phenylcadmium reagent and 0.025 mol of bromo ester. Control experiments to determine the degree of racemization of bromo ester were carried out by measuring the optical rotation and glpc peak area before and after the addition of fresh (+)-bromo ester. It was concluded that recovered bromo ester had racemized to the extent of 9% (maximum) during the course of the reaction.

Reaction of Allyl Bromide with Phenylcadmium Reagent.—A solution of 6.05 g (0.05 mol) of allyl bromide in 10 ml of anhydrous ether was added dropwise with stirring to 0.1 mol of phenylcadmium solution diluted with 75 ml of dry ether. After spontaneous refluxing subsided (about 5 min), the mixture was heated to reflux for an additional 4 hr. It was hydrolyzed with 10 ml of water, whereupon the usual precipitate formed. The liquid was decantated from the solid, and the precipitate was washed twice with 25-ml portions of ether. The washings were combined with the decantate, dried with $MgSO_4$, and filtered, and the ether was removed. When a portion of the 2.60 ml of crude residue was injected onto a column (10% Carbowax, 130°), three major peaks besides ether were observed. The one at 2.4 cm had the same retention time as that of allyl bromide. One at 10.7 cm was isolated, and its ir spectrum was identical with that of 3-phenylpropene (Sadtler[10] Spectrum No. 13701). The ir spectrum of the large peak at 16.1 cm was identical with that of bromobenzene. The yield of 3-phenylpropene was 39%, as determined by peak enhancement.

Reaction of Benzyl Bromide with Phenylcadmium Reagent.—To 0.1 mol of phenylcadmium reagent in 75 ml of anhydrous ether, 8.55 g (0.05 mol) of benzyl bromide was added dropwise with stirring at room temperature. The mixture was maintained at reflux for 10 hr, and then hydrolyzed with 10 ml of water. A portion of the crude mixture isolated as above was injected onto the gc (Apiezon L, 150°); three peaks were observed at 1.8, 2.4, and 15.3 cm. The last exhibited an ir spectrum identical with that of diphenylmethane (Sadtler[10] Spectrum No. 3389). Its yield, as determined by the peak enhancement method, was 40%.

Reaction of Phenylcadmium Reagent with 3-Bromocyclohexene.—To 0.1 mol of phenylcadmium reagent in 75 ml of anhydrous ether, 8.05 g (0.05 mol) of 3-bromocyclohexene was added slowly with stirring. After reaction conditions and workup identical with those of allyl bromide, there was obtained 7.0 g (7.40 ml) of crude product. Glpc analysis (10% Carbowax, 150°) gave peaks for ether and starting halide and one at 23.4 cm. Its ir spectrum was that expected for 3-phenylcyclohexene: 3080, 3050 (ArH, C=CH), 1650 cm^{-1} (C=C). The yield (81%) of 3-phenylcyclohexene was established by the method of peak enhancement.

The above reaction of 3-bromocyclohexene with phenylcadmium reagent was repeated, and aliquots of the reaction mixture were removed at various time intervals, placed in a sample tube, and the esr spectrum taken. Aliquots were taken immediately after mixing of the reagents at room temperature, after 5 min of stirring at room temperature, after 0.5 hr of refluxing, and after 4 hr of refluxing. None of the spectra indicated the presence of radicals.

Reaction of Chloromethyl Methyl Ether with Phenylcadmium Reagent.—Reaction as above of a solution of 4.0 g (0.05 mol) of chloromethyl methyl ether in 10 ml of anhydrous ether and phenylcadmium reagent afforded 6.0 ml of crude product. On glpc (Apiezon L, 160°) it exhibited peaks for ether and benzene and one at 7.5 cm. The ir spectrum of the third peak was identical with that of commercial benzyl methyl ether (Sadtler[10] Spectrum No. 17013). The yield, determined by the peak enhancement method, was 34%. No starting material or other by-products were found.

Registry No.—Phenylcadmium reagent, 15924-35-3; ethyl α-bromopropionate, 535-11-5; ethyl α-bromoisobutyrate, 600-00-0; (*R*)-(+)-methyl α-bromopropionate, 20047-41-0; allyl bromide, 106-95-6; benzyl bromide, 100-39-0; 3-bromocyclohexene, 1521-51-3; chloromethyl methyl ether, 107-30-2.

(15) H. Janssen, *Justus Liebigs Ann. Chem.*, **250**, 125 (1889).

Noble Metal Catalysis. II. Hydratocarbonylation Reaction of Olefins with Carbon Monoxide to Give Saturated Acids

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A process study of the hydratocarbonylation reaction of olefins with carbon monoxide to give saturated acids is described. The catalyst is probably a zero valent palladium–phosphine complex. Effects of changes in temperature, pressure, and concentrations of the three reactants and the complex catalyst system were studied. The rate of reaction depends approximately in a linear manner on the concentration of olefin and the pressure of carbon monoxide, while the rate reaches a maximum with a water concentration of 5–10%. The catalyst system undergoes a complex number of changes between the zero and plus two valence states, probably some involving the carbon moieties attached to the phosphine ligand.

The synthesis of saturated carboxylic acids from olefins, carbon monoxide, and water has been recently described,[1] according to eq 1 using a palladium–phosphine complex as catalyst.

$$RCH{=}CH_2 + CO + H_2O \xrightarrow{\text{cat.}} RCH_2CH_2CO_2H + CH_3CHRCO_2H \quad (1)$$

If alcohols are used in place of water, then esters are produced.[2] These palladium–phosphine catalyzed systems have advantages in rate and selectivity over the earlier palladium complexes without phosphines.[3] However, in those examples involving α olefins the branched-chain isomer was shown to be dominant.[2,4] The purpose of this paper is to describe methods for obtaining increased yields of the straight-chain acids starting from α olefins, since the straight-chain acids find greater utility as surface active agents.

Results

The following variables were studied: temperature and pressure, catalyst and solvent changes, proportions of olefin and water, and oxidation–reduction conditions.

(1) N. von Kutepow, K. Bittler, and D. Neubauer, U. S. Patent 3,437,676 (1969), to Badische Anilin- and Soda-Fabrik.

(2) K. Bittler, N. von Kutepow, D. Neubauer, and H. Reis, *Angew. Chem., Int. Ed. Engl.*, **7**, 329 (1968).

(3) J. Tsuji, M. Morikawa, and J. Kiji, *Tetrahedron Lett.*, 1937 (1963).

(4) R. Huttel, *Synthesis*, **5**, 225 (1970).

Effect of Olefin.—1-octene was chosen as the olefin component because of its ready availability and purity (over 90% 1-octene) and because it might suitably represent olefins used for fatty acid synthesis. The results are shown in Table I. At both 125 and 150°

TABLE I
CONVERSION TO AND RATIO OF ACID PRODUCTS AS A FUNCTION OF WEIGHT OF STARTING OLEFIN

Starting wt 1-Octene, g[a]	Temp, °C	Conversion, %	Ratio normal acid to α-methyl acid
80	125	72	1.7
160	125	80	1.5
40	150	71	0.7
80	150	75	0.5
160	150	74	0.5

[a] Water was added intermittently to keep water percentage around 5%. Otherwise except where noted conditions were as for the "standard run"; see Experimental Section.

increases in the 1-octene concentration lead to increases in the production of acids. The small changes in normal to α-methyl acid ratio may be due to small changes in the water concentration and/or catalyst changes (as discussed later). The production of acids is approximately proportional to the concentration of 1-octene.

Effects of Changes of Carbon Monoxide (and Hydrogen) Pressure.—As might be expected, increases in the carbon monoxide pressure cause increases in the yield of acid products. The increase is approximately linear with increase in carbon monoxide pressure. However, the ratio of normal to α-methyl acid products is effected inversely; *i.e.*, as carbon monoxide pressure increases the ratio decreases; refer to Table II.

TABLE II
CONVERSION TO AND RATIO OF ACID PRODUCTS AS A FUNCTION OF CARBON MONOXIDE (AND HYDROGEN) PRESSURE

Pressure, psig		Conversion, %	Ratio normal acid to α-Methyl acid
Carbon monoxide	Hydrogen		
100	0	14	5.5
200	0	51	3.0
800[a]	0	71	2.0
350	50	76	3.6
750	50	74	2.1
700	100	78	2.5
400	400	33	3.8

[a] Standard run.

The effect of hydrogen is noteworthy.[5] Small partial pressures lead to an increase in yield and also ratio but ultimately the yield drops dramatically, but no aldehydes, esters, or alcohols were discerned as long as carbon monoxide pressures above 400 psig were maintained. At 200 psig carbon monoxide pressure (with no added hydrogen) some *n*-octane was found in the remaining olefin.

Effect of Changes in Water Concentration.—As can be seen from Table III, water has a most pronounced effect on both yield and product ratio. The water percentages listed (by weight) are for the initial water concentrations. A 100% yield of acid products corresponds to about a 4% drop in water concentration.

(5) D. M. Fenton, U. S. Patent 3,641,074 (1972), to Union Oil Company of California.

TABLE III
CONVERSION TO AND RATIO OF ACID PRODUCTS AS A FUNCTION OF INITIAL WATER PER CENT

Initial water %[a]	Temp, °C	Conversion, %	Ratio normal acid to α-methyl acid
50	125	38	2.0
12	125	80	0.9
8	125	74	1.5
4[b]	125	71	2.0
0	125	48	2.5
−50[c]	125	0	
75	150	11	0.9
22	150	57	0.8
12	150	64	0.5
8	150	73	1.0
0	150	63	2.0

[a] Standard catalyst and conditions except for water concentration. [b] Standard run. [c] 50% by weight acetic anhydride.

Thus, an initial water concentration of 0% means that anhydrides are the products of reaction. The yield of acid products reaches a maximum between 5 and 15% water both at 125 and 150°, while the ratio of normal acid to α-methyl acid reaches a minimum at slightly higher water levels. At quite high water levels probably a two-phase system exists, so that in the olefin-rich phase the concentration of water may be low, similar to the low water experiments. Thus the ratios of normal to α-methyl acids are similar, though the yields in the high concentration water experiments are low, probably owing to loss of catalyst. On the other hand, high anhydride levels also impede the reaction. It may be that a water molecule is a highly desirable ligand and at high anhydride concentrations it is lost. In a related system for hydratocarbonylation using a platinum–stannous chloride complex as catalyst, Kehoe and Schell[6] showed that small amounts of water were necessary for reaction even in alcoholic systems.

Effect of Temperature Changes.—The maximum yield of acids is obtained around 150° while the maximum ratio occurs around 125°. Yields at temperatures above 150° are complicated by the inverse reaction, *i.e.*, the dehydratocarbonylation reaction. At these temperatures acid products can be converted back to olefin, carbon monoxide, and water so that both the forward reaction (hydratocarbonylation) and the reverse reaction (dehydratocarbonylation) occur at appreciable rates. The resulting ratios and conversion are a function of both reactions; refer to Table IV.

TABLE IV
CONVERSION TO AND RATIO OF ACID PRODUCTS AS A FUNCTION OF TEMPERATURE

Temp, °C	Conversion, %	Ratio normal acid to α-methyl acid
100	47	1.3
125[a]	71	2.0
150	76	1.2
175	71	1.0

[a] Standard run.

Effects of Varying Catalyst Concentrations.—When the standard catalyst (0.5 g of palladium chloride and 3 g of triphenylphosphine, a molar ratio of 1:4) is doubled, the conversion of acid products goes from 71% to 77%

(6) L. J. Kehoe and R. A. Schell, *J. Org. Chem.*, **35**, 2846 (1970).

but the ratio of acid products remains constant at 2.0. However, if just the triphenylphosphine concentration is increased, then there are effects on both conversion and ratio. At 125° the conversion is lowered by increasing the triphenylphosphine amount to 10 g but the ratio is dramatically increased, while at 150° both the yield and the ratio are increased. However, at 150°, additional increases in triphenylphosphine to 20 g increases the yield but lowers the ratio; refer to Table V.

TABLE V

CONVERSION TO AND RATIO OF ACID PRODUCTS AS A FUNCTION OF WEIGHT OF TRIPHENYLPHOSPHINE

Weight Triphenylphosphine, g	Temp, °C	Conversion, %	Ratio normal acid to α-methyl acid
3[a]	125	71	2.0
6[b]	125	77	2.0
10	125	46	3.5
3	150	75	1.0
10	150	80	3.6
20	150	86	1.5

[a] Standard run. [b] With 1 g of $PdCl_2$, 6 g of triphenylphosphine.

Effect of Phosphine Substituents.—Although all of the listed triarylphosphines are active it appears that electron-donating groups both decrease conversion and lower ratio. Tris-*o*-tolylphosphine is an exception and will be discussed later. *p*-Fluoro substituents give mixed results; refer to Table VI.

TABLE VI

CONVERSION TO AND RATIO OF ACID PRODUCTS AS A FUNCTION OF PHOSPHINE SUBSTITUENTS

Phosphine substituents[a]	Conversion, %	Ratio normal acid to α-methyl acid
Tris-*p*-anisyl	50	1.0
Tris-*p*-tolyl	67	1.2
Tris-*m*-tolyl	69	1.6
Triphenyl[b]	71	2.0
Tris-*o*-tolyl	73	2.4
Triphenyl[c]	77	2.0
Diphenyl-*p*-fluorophenyl[c]	81	1.8
Bis-*p*-fluorophenylphenyl[c]	83	1.7
Tris-*p*-fluorophenyl[c]	53	1.8

[a] 3 g of phosphine used in otherwise standard run. [b] Standard run. [c] 1 g of $PdCl_2$ and 6 g of triarylphosphine.

Effect of Additional Reagents.—Since both hydrochloric acid and lithium chloride reduce the normal to α-methyl ratio by the same amount, it is inferred that the effect on ratio is predominantly due to the chloride ion. Chloride ion (from lithium chloride) increases the conversion but hydrochloric acid decreases the conversion. So it must be that strong acid hydrogen ion is more detrimental to conversion than chloride ion is beneficial. In contrast to lithium chloride, those reagents capable of chloride ion removal, such as iron carbonyls, increase ratio but decrease conversion. Of course, iron carbonyls like ferrous chloride may complex with the palladium.[7] Stearic acid is effective, probably acting on colloidal palladium as a surface-active agent;[8] refer to Table VII.

(7) D. M. Fenton, U. S. Patent 3,661,949 (1972), to Union Oil Company of California.

(8) D. M. Fenton, U. S. Patent 3,530,155 (1970), to Union Oil Company of California.

TABLE VII

CONVERSION TO AND RATIO OF ACID PRODUCTS IN THE PRESENCE OF ADDITIONAL REAGENTS

Reagent	Amount of reagent, g	Conversion, %	Ratio normal acid to α-methyl acid
Concd HCl	2	69	1.6
$LiOAc \cdot 2H_2O$	5	74	2.0
LiCl	5	82	1.6
Stearic acid	10	86	1.0
$FeCl_2 \cdot 4H_2O$	5	62	0.9
$Fe(CO)_5$	2	50	3.0
$Fe_2(CO)_9$	2	57	2.6
a	0	71	2.0

[a] Standard run.

Effect of Solvents.—Acetic acid was chosen as the paramount solvent because of its convenience. However, in industrial practice the product acids would probably be chosen as solvents. At 150° or lower the reverse reaction is negligible; so other carboxylic acids can be used. Noncarboxylic acid solvents that have a capacity for dissolving water may also be used; refer to Table VIII.

TABLE VIII

CONVERSION TO AND RATIO OF ACID PRODUCTS PRODUCED IN OTHER SOLVENTS

Solvent	Temp, °C	Conversion, %	Ratio normal acid to α-methyl acid
Valeric acid	125	58	2.2
	150	40	1.3
Octanoic acid	125	28	0.5
Tetrahydrofuran	125	28	0.8
Pyridine	150	0	
Acetonitrile	150	~44	0.7

Effect of Oxidative Conditions.—It was found necessary to thoroughly purge the system of oxygen in order to obtain reproducible results, for oxygen dramatically lowered the rate of conversion. Other oxidizing agents, such as benzoquinone and cupric chloride, completely inhibited the reaction. Also it was found that, when triphenylphosphine oxide was substituted for triphenylphosphine while under oxygen-free conditions, the hydratocarbonylation reaction did proceed but at diminished rate. Therefore, the conversion of triphenylphosphine to triphenylphosphine oxide was not the only reason for inhibition. Since hydroquinone, the reduction product of benzoquinone, actually increased the rate of reaction, and since zero-valent palladium complexes were observed as the products of the initial palladium complex added to the reaction, *e.g.*, $PdCl_2[(C_6H_5)_3P]_2$ (I), then it is proposed that the interfering oxidizing agents complex with I and render it inactive.

Effect of Reducing Agents.—Moderate amounts of reducing agents, *e.g.*, hydrogen, hydrazine, and hydroquinone, cause slightly improved conversion, and in the case of hydrogen to slightly higher ratios. The improved conversions may be due to the impedance of the oxidative side reaction leading to the inactive complex I. Previously Tsuji[9] noted that with the nonphosphine complexes hydrogen was beneficial. It was noted that in an open flask at 110° I was stable in acetic acid with 1-octene and that the introduction of carbon monoxide

(9) J. Tsuji and K. Ohno, *Advan. Chem. Ser.*, **No. 70**, 155 (1968).

TABLE IX
PALLADIUM COMPLEXES ISOLATED FROM HYDRATOCARBONYLATION REACTIONS

Registry no.	Complex	Decomposition range, °C	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Phosphorus, % Calcd	Phosphorus, % Found	Chlorine, % Calcd	Chlorine, % Found
13965-03-2	$PdCl_2[P(C_6H_5)_3]_2$	280–290	61.6	61.1	4.3	4.8	8.8	8.6	10.0	8.7
40691-26-7	$PdCl(O_2CCH_3)[P(C_6H_5)_3]_2$	250–260	63.1	63.4	4.6	5.7	8.5	8.4	4.9	5.5
28516-49-6	$Pd[P(C_6H_5)_3]_3$	90–100	72.7	71.6	5.1	5.6	10.0	10.2	0.0	<0.1
14221-01-3	$Pd[P(C_6H_5)_3]_4$	105–110	74.8	75.2	5.2	5.5	10.7		0.0	
40691-27-8	$Pd[P(C_6H_5)_3]_2[(C_6H_5)_2PC_6H_4Cl]$	120–130	69.0	70.6	4.9	4.9	10.3	10.1	4.0	4.5
40756-38-5	$Pd[P(C_6H_5)_3][(C_6H_5)_2P(C_6H_4Cl)]_2$	120–130	66.6	66.7	4.7	5.0	10.0	9.6	7.6	7.4
40691-28-9	$PdCl_2[(C_6H_5)P(C_6H_4Cl)_2]_2$	200–210	51.5	50.4	3.1	3.9	7.4		25.4	26.7
40691-29-0	$PdCl_2[C_6H_5P(C_6H_4Cl)_2][P(C_6H_4Cl)_3]$	290–300	49.7		2.9		7.1	6.0	28.2	28.1

only very slowly caused catalyst decomposition, while either hydrogen or hydrazine quickly reduced I. Also small amounts of lithium acetate slightly speeded up the decomposition of I.

The slightly increased normal to α-methyl ratio with small amounts of hydrogen may be due to the reaction of hydrogen with complexes such as V (see next section) to give back complex I and thus impede the formation of substituted chlorophenylphosphine complexes which may give ratios more like fluorophenylphosphine complexes, *i.e.*, less than 2. Indeed it was noted for the standard run that in the first 0.5 hr the ratio was 2.4 with subsequent leveling off at 2.0.

Discussion of the Catalyst System.—The palladium catalyst system undergoes many complex reactions. When hydrochloric acid was added to the standard run, the main catalyst component isolated after reaction was I, as was noted earlier.[2] However, in other experiments without the added hydrochloric acid I was not isolated. Several components were isolated and will be discussed.

In those runs deficient in phosphine, colloidal palladium metal was sometimes found. This palladium metal could be redissolved by treating it with hydrochloric acid and triphenylphosphine[10] in acetic acid according to eq 2, and accordingly hydrogen was de-

$$Pd^0 + 2HCl + 2(C_6H_5)_3P \longrightarrow I + H_2 \qquad (2)$$

tected in the gas phase above the reaction. Small amounts of hydrogen were also detected in the gas phase during the hydratocarbonylation reaction, particularly if hydrochloric acid was present. It may also be recalled that with low carbon monoxide concentrations some conversion of octene to octane occurred.

It was also found that heating I to its decomposition point under vacuum gave an equimolar mixture of triphenylphosphine and chlorophenyldiphenylphosphine. This is germane, for, particularly from experiments conducted above 150° and in the presence of excess chloride ion, there were isolated type II complexes where

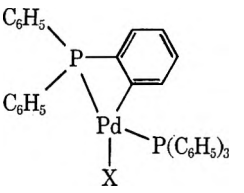
$PdCl_2[P(C_6H_{5-x}Cl_x)_3]_2$ II $Pd[P(C_6H_{5-x}Cl_x)_3]_3$ III

x = 0 and/or 1. The infrared spectrum of some of these yellow-orange complexes showed aromatic ortho disubstitution, indicating that the chlorine was ortho to the phosphorus. Some of these complexes are listed in Table IX.

The known complex[11] $Pd[P(C_6H_5)_3]_3$ was frequently isolated, particularly at high triphenylphosphine concentrations. Also $Pd[P(C_6H_5)_3]_4$ was once isolated.[12] The corresponding chlorophenylphosphine complexes III were isolated, where x = 0 and/or 1. These light yellow complexes slowly turned green on standing and were probably picking up oxygen.[13] In addition, small amounts of triphenylphosphine oxide and, under strongly acidic conditions, some diphenylphosphinic acid were found.

With a lithium acetate cocatalyst IV and V were

$PdCl(O_2CCH_3)[P(C_6H_5)_3]_2$
IV



V, X = Cl, OH, O_2CCH_3

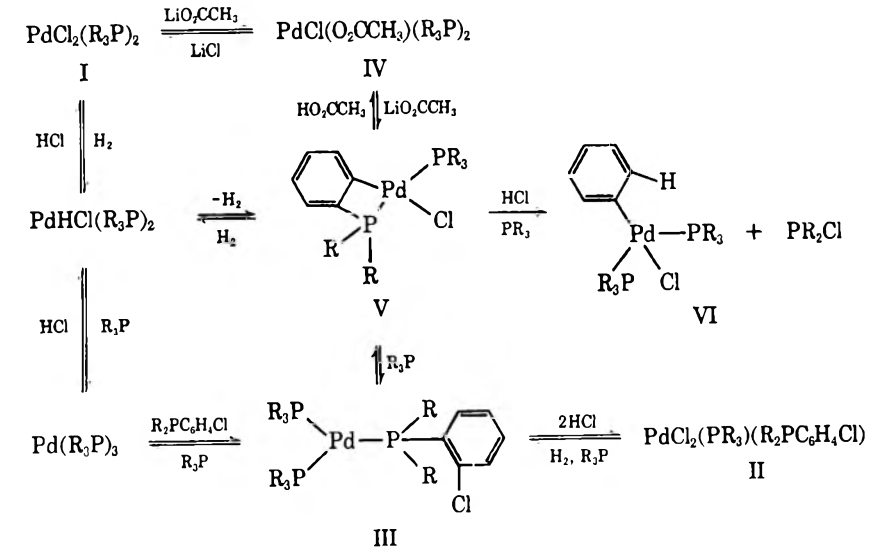
found. V is quite labile and was not isolated in satisfactory condition from hydratocarbonylation runs, but can be made independently (see Experimental Section). The addition of hydrochloric acid to V gives I. Also it was shown that $Pd[P(C_6H_5)_3]_4$ reacts with chloride to give V (X = Cl). Also V in the presence of excess triphenylphosphine goes to type III complexes. Furthermore, Coulson[14] reported that the decomposition of a mixture of palladium chloride and $Pd[P(C_6H_5)_3]_4$ gave VI, which might arise from still another decomposition mode of V. Scheme I shows some of the interrelationships proposed for the complex catalyst system. Although the analogous platinum complexes to V are known, apparently V cannot be recovered by simple heating of I; so bases are necessary (however, see Shaw[15]). The addition of hydrogen effects reduction while that of hydrogen chloride causes oxidation (dehydrogenation). Also base hinders oxidation. The insertion of palladium into a carbon–chlorine bond effects oxidation and the reverse reaction causes reduction of the palladium.

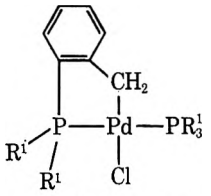
Tris-*o*-tolylphosphine is a special case. The palladium complex of this ligand does not give V complexes but instead VII is formed. The results of these various effects are summarized in Table X.

Dehydratocarbonylation and Reversible Reactions.—An important adjunct to the hydratocarbonylation reaction is the dehydratocarbonylation, which involves the

(10) J. Tsuji and K. Ohno, *J. Amer. Chem. Soc.*, **90**, 94 (1968).
(11) L. Malatesta and M. Angoletta, *J. Chem. Soc.*, 1186 (1957).
(12) P. Fitton, M. P. Johnson, and J. E. McKeon, *Chem. Commun.*, **1**, 6 (1968).
(13) C. J. Nyman, C. T. Wymore, and G. Wilkinson, *J. Chem. Soc. A*, 561 (1968).
(14) D. R. Coulson, *Chem. Commun.*, **23**, 1530 (1968).
(15) A. J. Cheney and B. L. Shaw, *J. Chem. Soc., Dalton Trans.*, 860 (1972).

SCHEME I





VII, R^1 = *o*-tolyl

TABLE X

Effect[a]	Change made by increasing the effect: Rate changes	Ratio changes
HCl	Minor decrease	Lower
LiO_2CCH_3	Minor increase	None
LiCl	Increase	Lower
Low chloride	Decrease	Higher
Carboxylic acid solvent	Increase	Higher
Water	Maximum at initial concn around 8%	Maximum at initial concn around 4%
Temperature	Maximum at 150°	Maximum at 125°
1-Octene	Increase	None
Carbon monoxide	Increase	Lower
Hydrogen	Maximum at 50 psig	Higher
Triphenylphosphine	Reaches maximum	Possible maximum
Other phosphines	Complex, generally lower	Complex, generally lower

[a] As compared to standard run.

decomposition of acids back to olefins, carbon monoxide, and water.[16] Under certain conditions both of these reactions are significant so that products are based on thermodynamic control, and equilibrium conditions dominate. On the other hand, conditions are easily found where only one of the two reactions is occurring to any significant extent, so that kinetic control is achieved. Further, if only one acid isomer is desired, the other can be separated by distillation, crystallization, clathration, etc., and submitted to dehydratocarbonylation conditions to give back the olefin starting material. In this way, by-products are eliminated and essentially only the desired product is synthesized.[17]

(16) D. Fenton, U. S. Patents 3,530,198 (1970), 3,578,688 (1971), and 3,592,849 (1971), to Union Oil Company of California.

(17) D. Fenton, U. S. Patent 3,668,249 (1972), to Union Oil Company of California.

Proposed General Mechanism.—Since the rate of formation of acid products near standard reaction conditions depends on the concentration of all three of the reactants, *i.e.*, 1-octene, carbon monoxide, and water, as well as the complex catalyst system, then the catalyst system must accommodate all three of the reactants before the rate-determining step. It will be recalled that acid production varies linearly with both 1-octene and carbon monoxide concentrations but that only carbon monoxide has an effect on ratio. Similarly, near standard conditions acid synthesis is approximately proportional to water concentration, and, like carbon monoxide, water also effects the acid ratio. Thus it is inferred that, in addition to the three reacting molecules, the active complex also includes other ligands, which list includes carbon monoxide and water, but not 1-octene. It should be emphasized that the competition of nonreactive ligands for the remaining sites of the palladium complex is equilibrium controlled and depends not only on ligand concentration but also on the stability of the palladium–ligand bond. In particular, since quite small amounts of both water (or hydroxide ligand) and chloride have such pronounced effects, it is evident that they form exceptionally stable ligand–palladium bonds. However, chloride, like 1-octene, does not effect ratio (except for a slight initial drop). On the other hand, the effect of triphenylphosphine is complex and ratios vary dramatically. It is concluded that the list of important ligands filling nonreactive sites on the active palladium complex includes chloride, water (or hydroxide), carbon monoxide, and triphenylphosphine, but it is only the last three that significantly affect ratio and particularly the last two. Since increases in the triphenylphosphine concentration lead first to an increase in ratio and then to a decrease, this implies that at high triphenylphosphine concentrations two triphenylphosphines are complexed at one time.

The transition state might look more like the product than like the starting materials. That this is true can be deduced from the following. The reaction of olefins, carbon monoxide, and ROH for the production of esters, acids, and anhydrides has shown to be reversible,[16] and also the production of esters occurs at lower temperatures than does the production of acids, while the for-

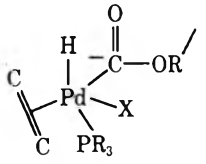
mation of anhydrides at practical conversions is difficult. Vice versa, the decomposition of anhydrides is facile at 150° while acids need temperatures around 200° and esters demand still higher temperatures. Thus the nature of R in VIII and IX is important. If the degree of ionization is important, then the formation of products should decrease in the order of acids > esters, but such is not the case. Also, if the production of the oxygen–hydrogen bond in ROH is important in the decomposition reactions then the decomposition series should be esters > anhydrides > acids, and again such is not the case. Therefore, the nature of R in ROH is not so important as the nature of R in RO_2CR', or, in other words, the transition state more closely resembles the acid derivative product than it does olefin, carbon monoxide, and ROH. While this fact does not rule out a concerted mechanism, it does imply that a stepwise mechanism is possible.

There are several candidates for the first step in the stepwise mechanism. Palladium–olefin[18] and palladium–carbonyl[19] complexes are known as well as alkyl,[12,19,20] acyl, and carboalkoxyl[12,21] complexes. Tsuji[22] and Chatt[23] have discussed mechanisms in which first-formed alkyl complexes are converted next to acyl complexes and finally to product. Heck[24] and the author[25] have considered the addition of carboalkoxyl or carboxyl complexes to olefins.

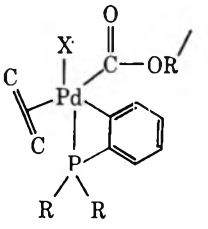
Mitigating against alkyl complexes is the fact that neither in the presence or absence of carbon monoxide were any alcohols (olefin plus water) or esters (olefin plus carboxylic acid) found, except under very acidic conditions with mineral acid. This is in contrast to palladium(II) chemistry, where acetaldehyde and vinyl carboxylates are prepared. Recently McKeon[26] has emphasized this difference between Pd(II) and Pd(0) where Pd(II) will cause transesterification and transetherification reactions while reduced palladium will not, thus indicating that reduced palladium will not form alkyl–palladium bonds by addition to olefins[27] under non-strong-acid conditions. Also, in the presence of hydrogen no aldehydes are produced, thus mitigating against acyl complexes although at still higher hydrogen (and lower carbon monoxide) pressures some alkane is produced. If then we have eliminated, as the first step, the attachment of H to olefin as well as the attachment of carbon monoxide to olefin, then we have left to consider only the attack of ROH on the palladium–carbonyl complex. This complex could look like VIII.

Here pentacoordinate complexes are drawn, because although three ligands are donating two electrons each, the H and COR are donating only two electrons altogether.[28] The olefin may be coplanar with the ring.[29]

The nature of R′ in type VIII complexes is important and it might be anticipated that esters would give more stable complexes than acids and acids more stable complexes than anhydrides. In particular, carboxyl complexes can undergo the shift reaction to give carbon dioxide and hydrogen. This may also account for the small amounts of hydrogen found. That carboalkoxyl complexes are stable was shown for Pd(II) complexes when oxalates[30] were prepared from carbon monoxide and alcohols, but in an aqueous environment oxalic acid could not be, and only carbon dioxide was produced. Thus Pd(II) can tolerate two carbonyl groups, at least one of which is a carboalkoxyl group.



VIII, X = Cl



IX, X = Cl, H

The hydride ligand in type VIII complexes may be relatively unstable. It has been shown that other palladium hydrides are unstable either under acidic or basic conditions,[31] and only moderately thermally stable.[32]

Under these conditions reactions like those discussed in Scheme I are probably occurring. In particular, complexes like IX could occur. This might account for the interesting effects of mixed phosphines. With the phenyl-substituted phenylphosphines it may be that the phenyl group is the preferred "second" ligand and thus exerts an extraordinary influence.

The second step would then be the attack of the olefin on the carboxyl group to give β-carboxyalkyl–palladium complexes. The ultimate formation of either the straight-chain acid of the branched-chain acid is determined in this step. Steric effects would dictate the formation of the straight-chain acid, and this is the general result as long as large amounts of free mineral acid are absent (in the presence of free mineral acid alkyl–palladium complexes are probably formed from alkyl groups which, in turn, are formed by the addition of a proton to the olefin so that the direction of proton addition determines the ratio).

That intermediates have some lifetime was indicated when it was shown that in competitive experiments the rate of isomerization of butyric anhydride to isobutyric anhydride was faster than the rate of reaction of butyric anhydride with 1-octene to give nonanoic and α-methyloctanoic acids (anhydrides). The reverse reaction with nonanoic anhydride and propylene also showed that isomerization was faster than olefin exchange.[33]

Finally, the addition of the olefin to the carboxyl

(18) R. Van Der Linde and R. O. De Jongh, *Chem. Commun.*, **11**, 563 (1971); C. A. Tolman, W. C. Seidel, and D. H. Gerlach, *J. Amer. Chem. Soc.*, **94**, 2669 (1972).

(19) A. Misono, Y. Uchida, M. Hidai, and K. Kudo, *J. Organometal. Chem.*, **20**, 7 (1969); K. Kudo, M. Hidai, and Y. Ochida, *ibid.*, **33**, 393 (1971).

(20) P. Fitton and E. A. Rick, *J. Organometal. Chem.*, **28**, 287 (1971).

(21) S. Otsuka, M. Naruto, T. Yoshida, and A. Nakamura, *J. Chem. Soc., Chem. Commun.*, 396 (1972).

(22) J. Tsuji, K. Ono, and T. Kajimoto, *Tetrahedron Lett.*, 4565 (1965).

(23) G. Booth and J. Chatt, *J. Chem. Soc. A*, 634 (1966).

(24) R. F. Heck, *J. Amer. Chem. Soc.*, **93**, 6896 (1971).

(25) D. M. Fenton and K. L. Olivier, *Chemtech*, 220 (1972).

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(31) E. H. Brooks and F. Glocking, *J. Chem. Soc. A*, 1030 (1967).

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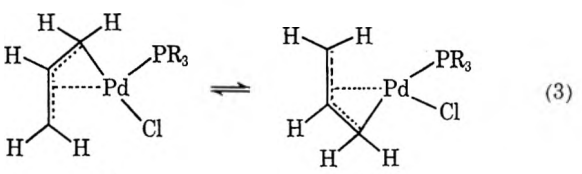
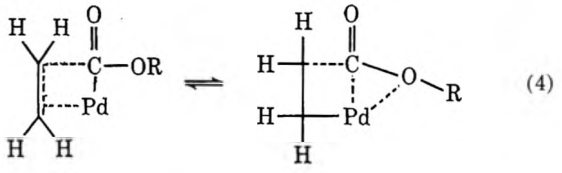
group can be linked to the π–σ complex shifts of allyl palladium complexes,[34] where eq 3 shows the π–σ



(3)



(4)

shifts and eq 4 shows the corresponding form for the reversible hydratocarbonylation reaction.

Experimental Section

A one-half gallon stainless steel stirred autoclave equipped with a cooling coil and condenser was used for the hydratocarbonylation reactions. The catalyst system, solvent, water, and olefin were placed in the autoclave, which was then purged twice with nitrogen. Carbon monoxide was added to the desired pressure. Heating and stirring were started. Pressure drops were noted. The autoclave was cooled and depressured, and any gain or loss of liquid weight was noted. The contents were analyzed by gas chromotography on a FFAP (free fatty acid phase) coated column. Each sample was run twice to reduce problems associated with "memory" effects. When acetic acid was used as solvent, additional information was obtained by either concentration by partial evaporation or by water washing. The recipe for the standard run is as follows: palladium chloride·$2H_2O$, 0.5 g; triphenylphosphine, 3 g; acetic acid, 400 ml; water, 15 g; 1-octene, 80 g; carbon monoxide, 800 psig. The conditions for the standard run are as follows: temperature, 125°; pressure, 800 psig (initial); time, 2 hr. In addition to the production of straight-chain and α-methyl acids there were also obtained small amounts of two other isomeric acids. Without additional hydrochloric acid the total of these other acids (α-ethylheptanoic and α-propylhexanoic) was less than 20% of the α-methyloctanoic acid production.

Preparation of V (R = C_6H_5).—To a 100-ml saturated solution of palladium chloride bis(triphenylphosphine) in *N*,*N*-dimethylformamide (the filtrate from 2.5 g of palladium chlorine bis(triphenylphosphine) in 100 ml of *N*,*N*-dimethylformamide), all protected by a nitrogen atmosphere, was added a 10-ml solution of 0.5 g of lithium acetate in 20 ml of water. Quickly a light yellow solid precipitated, decomposition range 80–100°. *Anal.* Calcd for $C_{36}H_{29}ClP_2Pd$: C, 65.5; H, 3.7; P, 9.4; Cl, 5.4. Found: C, 65.7; H, 4.4; P, 9.4; Cl, 5.3. The infrared spectrum showed ortho substitution and the compound could be reduced polarographically.

Conversion of V to Pd[P(C_6H_5)$_3$]$_3$.—To 1.5 g of V (R = C_6H_5) and 3 g of triphenylphosphine was added 200 ml of ethanol. The mixture was stirred for 6 hr at room temperature in a closed container. A white solid appeared. *Anal.* Calcd for $C_{54}H_{45}P_3Pd$: C, 72.6; H, 5.1; P, 10.4; Cl, 0.0. Found: C, 71.3; H, 5.2; P, 10.2; Cl, 0.3.

Reaction of V with Carbon Tetrachloride. Formation of II (Where Only 1 X = 1, Other X = 0).—To a solution of 1.5 g of V (R = C_6H_5) in 50 ml of carbon tetrachloride was added heat to reflux for 5 min. A yellow solid formed. *Anal.* Calcd for $C_{36}H_{29}Cl_3P_2Pd$: C, 58.7; H, 4.0; Cl, 14.4. Found: C, 59.2; H, 4.6; Cl, 13.0.

Reaction of V with Bromine.—Bromine (0.7 g) was slowly added to a solution of V (1.5 g) in benzene (50 ml). At first the color was rapidly discharged but after about half of the bromine was added the color persisted. The solution was refluxed for 5 min. To the cooled solution was added 50 ml of methanol, which caused the precipitation of 0.5 g of $PdBr_2[P(C_6H_5)_3]_2$, decomposition range 300–305°. The filtrate was concentrated on the steam bath to give brick red solid, 0.7 g, analyzing for either $PdBr_2[P(C_6H_5)_2(C_6H_4Br)]_2$ (*Anal.* Calcd for $C_{36}H_{28}Br_4P_2Pd$: C, 45.6; H, 3.0; P, 6.5.) or $PdBr_2[P(C_6H_5)(C_6H_4Br)_2][P(C_6H_5)_2C_6H_4Br]$ (*Anal.* Calcd for $C_{36}H_{27}Br_5P_2Pd$: C, 42.1; H, 2.7; P, 6.0. Found: C, 43.1; H, 3.4; P, 5.9).

Conversion of Pd[P(C_6H_5)$_3$]$_3$ to Pd[P(C_6H_5)$_3$]$_2$[P(C_6H_5)$_2$-C_6H_4Cl].—To 2 g of $PdCl_2[(C_6H_5)_3P]_2$, 2 g of triphenylphosphine, and 200 ml of 1-butanol was added 5 ml of hydrazine hydrate. The mixture was magnetically stirred and heated to 90°, whereupon the white $Pd[P(C_6H_5)_3]_3$ formed. Heating was continued until a greenish-yellow precipitate had formed, decomposition range 125–130°. *Anal.* Calcd for $Pd[(C_6H_5)_3P]_2[(C_6H_5)_2PC_6H_4Cl]$: C, 67.4; H, 5.2; P, 10.9; Cl, 4.1. Found: C, 69.1; H, 5.2; P, 10.6; Cl, 2.0.

Conversion of V to I (R = C_6H_5).—To 0.8 g of V (R = C_6H_5), 5 ml of concentrated hydrochloric acid, and 1 g of triphenylphosphine in a 250-ml flask was added 100 ml of acetic acid. The mixture was refluxed for 16 hr to give a yellow precipitate identified as I, decomposition range 300–310°. *Anal.* Calcd for $C_{36}H_{30}Cl_2P_2Pd$: Cl, 10.1. Found: Cl, 9.8.

Preparation of IV (R = C_6H_5).—To 4 g of I (R = C_6H_5) dispersed in 200 ml of acetic acid was added 5 ml of hydrazine hydrate. The mixture was refluxed for 30 min. A light yellow solid was filtered away from the blackish filtrate, decomposition range 260–270°. *Anal.* Calcd for IV, $C_{38}H_{33}O_2ClP_2Pd$: C, 62.9; H, 4.6. Found: C, 63.8; H, 4.7.

Decomposition of I (R = C_6H_5).—To 3.5 g of I (R = C_6H_5) in 50 ml of acetic acid and 50 ml of acetic anhydride in a 250-ml flask was bubbled nitrogen while the mixture was heated to reflux for 6 hr. The palladium was removed and the filtrate was distilled to give 0.5 g of an oil, bp 220–240° (1 mm). The infrared spectrum of this distillate showed triphenylphosphine and an ortho-disubstituted phenyldiphenylphosphine. *Anal.* Calcd for 50% triphenylphosphine and 50% chlorophenyldiphenylphosphine: Cl, 6.0. Found: Cl, 5.2.

Preparation of VII.—To 3.5 g of palladium chloride bis(tri-*o*-tolylphosphine), 100 ml of acetic acid, and 5 g of lithium acetate in a 250-ml flask was added hydrogen while the mixture was heated for 2 hr at reflux. An orange-yellow precipitate was filtered which gave an infrared spectrum that indicated the presence of methylene groups (not present in the starting material). *Anal.* Calcd for VII, $C_{42}H_{41}P_2ClPd$: Cl, 4.7. Found: Cl, 5.7.

Registry No.—II, 40691-30-3; V, 35917-41-0; VII, 35917-43-2; 1-octene, 111-66-0; carbon monoxide, 630-08-0; triphenylphosphine, 603-35-0; carbon tetrachloride, 56-23-5; bromine, 7726-95-6; $PdBr_2[P(C_6H_5)_3]_2$, 23523-33-3; $PdBr_2[P(C_6H_5)_2(C_6H_4Br)]_2$, 40691-31-4; $PdBr_2[P(C_6H_5)(C_6H_4Br)_2][P(C_6H_5)_2(C_6H_4Br)]$, 40691-32-5; palladium chloride bis(tri-*o*-tolylphosphine), 40691-33-6.

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Substituted 1-Chlorophosphetanium Salts. Synthesis, Stereochemistry, and Reactions[1a]

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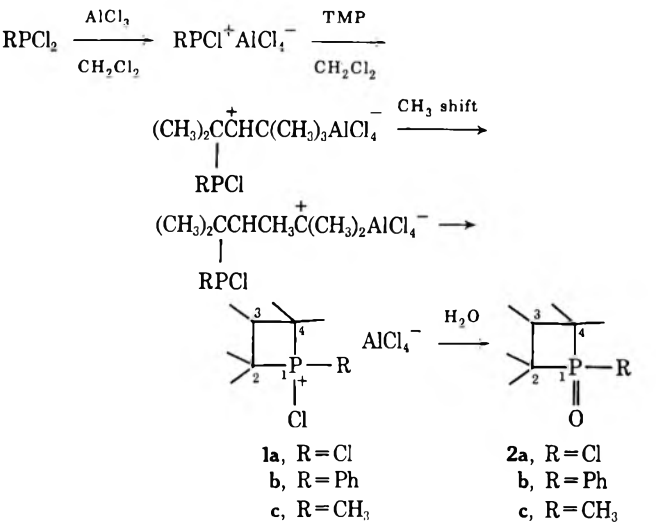
Received December 27, 1973

The phosphetanium tetrachloroaluminates **1b** and **1c** derived from $PhPCl_2$–$AlCl_3$ or CH_3PCl_2–$AlCl_3$, and 2,4,4-trimethyl-2-pentene have been isolated and fully characterized. The cis–trans isomer distribution in these salts has been correlated with the isomer ratio of the oxides **2b** and **2c** when the former are quenched with water. The experimental mode of water addition is critical and determines the isomeric composition; an explanation consistent with these observations is advanced. The three chlorinated adducts **11**, **10**, and **6** derived from 1-methyl-, 1-phenyl-, and 1-*tert*-butyl-2,2,3,4,4-pentamethylphosphetane have been prepared. The cis–trans isomers of these chlorides undergo interconversion in solution; the rate of stereomutation follows the order **10** faster than **11** faster than **6** at 35°. Trigonal bipyramidal intermediates (or transition states) are invoked to account for the isomer crossover. Interconversion can be frozen by addition of aluminum chloride to give **1b**, **1c**, or **7**. Thermolysis of the phosphetanium chlorides leads to ring-opened and ring-expanded products. Hydrogen bromide "adducts" of several phosphetane oxides have been synthesized, and the nature of their structure is discussed.

There are only a limited number of reports which have described the successful synthesis of the phosphetane ring system.[2] Of these, the addition of PCl_3–$AlCl_3$ to 2,4,4-trimethyl-2-pentene (TMP) to give **1a**[2c] (Scheme I) and its subsequent generalization[2f] have led to substituted phosphetanes which have been widely employed for stereochemical,[2f,g,3] kinetic,[3l,n] ^{13}C nmr,[3h–j,m] and other studies.[3k]

The mechanism suggested by McBride[2c] for the formation of **2a** (Scheme I) implied that **1a** was formed as an intermediate; however, the latter was not characterized at the time. Our initial observation[2f] that the cis:trans ratio of the products **2b** or **2c**[4] was dramatically dependent upon the mode of addition of water to **1b** or **1c** (see Table I) prompted us to isolate **1b**[5] and **1c** and to relate the stereochemistry of these intermediates to the corresponding oxides. The results of these and related experiments form the basis of the present investigation.

Scheme I



1a, R = Cl; **b**, R = Ph; **c**, R = CH_3 — **2a**, R = Cl; **b**, R = Ph; **c**, R = CH_3

Results and Discussion

Isolation of the Tetrachloroaluminate Salts.—Treatment of CH_3PCl_2– or $PhCl_2$–$AlCl_3$ in methylene chloride with TMP was carried out in the usual manner[2f] except that the intermediate salts were isolated prior to the addition of water. The reactivity of these compounds required the rigorous exclusion of atmospheric moisture and manipulation in dry solvents. The nmr of the crude reaction products **1b** or **1c** indicated the presence of two isomers in each case. The ^1H nmr of **1a** *in situ* showed a single isomer as anticipated from its structure. Isolation of the crystalline intermediates **1b** and **1c** followed by redissolution in CH_2Cl_2 did not change the original isomer ratio. The ^1H nmr spectra were similar to other phosphetanium salts[2f] and the low field ^{31}P shifts were in accord with values of chloro-substituted phosphonium salts;[6] addi-

(1) (a) This work was partially supported by Public Health Service Grant CA 11631, National Cancer Institute, and a grant from the Marquette University Committee on Research. (b) Alfred P. Sloan Research Fellow, 1971–1973.

(2) (a) G. M. Kosolapoff and R. F. Struck, *J. Chem. Soc.*, 3739 (1957); (b) M. Green, *ibid.*, 541 (1965); (c) J. J. McBride, Jr., E. Jungermann, J. V. Killheffer, and R. J. Clutter, *J. Org. Chem.*, **27**, 1833 (1962); (d) D. Berglund and D. W. Meek, *J. Amer. Chem. Soc.*, **90**, 518 (1968); (e) T. A. Zyablikova, A. P. Panteleeva, and I. M. Shermergorn, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 373 (1969); (f) S. E. Cremer and R. J. Chorvat, *J. Org. Chem.*, **32**, 4066 (1967); (g) G. Zon and K. Mislow, *Fortschr. Chem. Forsch.*, **19**, 88 (1971); (h) R. I. Wagner, U. S. Patent 3,086,053 (1963); *Chem. Abstr.*, **59**, 10124 (1963); (i) B. A. Arbuzov, L. A. Shapshinskaya, and V. M. Erokhina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1820 (1965).

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(4) An initial report[2f] indicated that the stereochemistry of **2c** was invariant with the mode of quench; a subsequent publication[3j] showed this to be incorrect. Also, the isomer ratios of **2b** in the earlier report[2f] were determined after recrystallization of the product; since fractionation occurs, these ratios differ from those in the present paper which records the ratios prior to recrystallization.

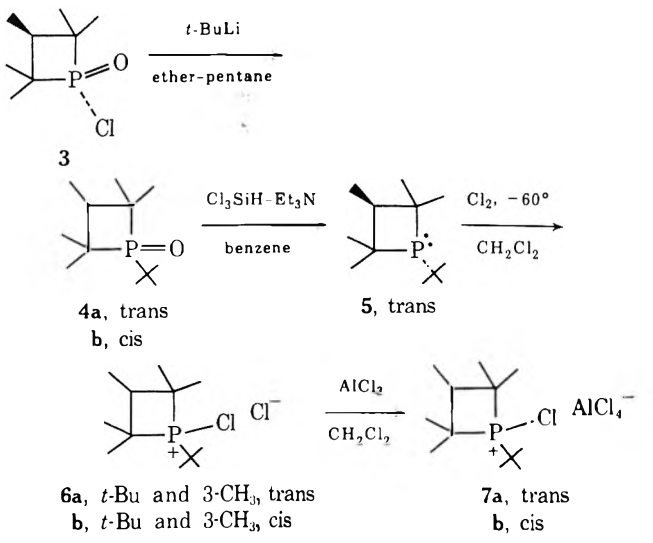
(5) A preliminary report on the isolation of **1b** has appeared: 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970, Abstract ORGN 62.

(6) A. J. Kirby and S. G. Warren in "The Organic Chemistry of Phosphorus," C. Eaborn and N. B. Chapman, Ed., Elsevier, Amsterdam, 1967, pp 26–27, 194; (b) J. R. Van Wazer, *et al.*, in "Topics in Phosphorus Chemistry," Vol. 5, M. Grayson and E. J. Griffith, Ed., Wiley-Interscience, New York, N. Y., 1967, Chapters 3 and 4.

tional structural support comes from ^{13}C nmr[3m] and satisfactory elemental combustion analysis.

A single attempt was made to prepare **7** from *tert*-butylphosphonous dichloride–aluminum chloride and TMP; the liquid product (after H_2O quench) did not show the characteristic nmr features[2f] of a phosphetane oxide. An alternate route for the preparation of **7** was achieved following Scheme II.

SCHEME II



The trans acid chloride **3**[7] was treated with *tert*-butyllithium to give **4a**; retention of configuration about phosphorus was expected from analogy to similar systems.[3d,8] The ^{13}C nmr spectrum supported[3j] the trans assignment. Reduction of **4a** to give **5** should also go with retention;[2f,3a] the ^{31}P shifts[8a] are consistent with this assignment. The phosphetane **5** was converted to **6a** with chlorine, and the latter gave **7a** with $AlCl_3$; the stereochemistry of **5** → **7a** is discussed under Chorination of the Phosphetanes.

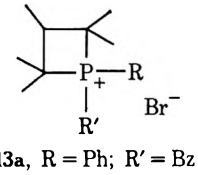
Chlorination of the Phosphetanes.—Our initial efforts were directed toward a stereospecific synthesis of the pure cis or trans isomers of **1b** and **1c** by an independent route. The availability of a predominance[2f] of *cis*- and *trans*-1-phenyl-2,2,3,4,4-pentamethylphosphetane (**8**) and 1,2,2,3,4,4-hexamethylphosphetane (**9**) suggested that **1b** and **1c** could be prepared by low-temperature chlorination and subsequent treatment with aluminum chloride as in the conversion of **5** to **7**. However, chlorination of a predominance of *either* the cis or trans isomers of **8** led to the same chlorinated product, **10**, which showed a remarkably simple nmr pattern of two overlapping doublets corresponding to the four C–CH_3 groups at carbons 2 and 4, a double doublet due to the C–CH_3 at carbon 3, a multiplet due to the hydrogen at carbon 3, and five aromatic protons. Likewise, chlorination of a predominance of the cis or trans isomers of **9** led to the same product whose nmr spectrum was considerably broadened but interpretable on the basis of the presence of two isomeric phosphetanium chlorides **11a**(**b**). The nmr spectrum of **10** is readily understood if the 1-phenylphosphetanium salts undergo rapid interconversion on the nmr time scale to give a simple, time-averaged spectum. In **11** the interconversion is slower, and the individual isomers are discernible, but as broadened peaks. Low-temperature nmr experiments support this explanation. At about −20° sharp nmr signals due to the separate isomers are observed in **10** as well as in **11**. Treatment of **10** and **11** in methylene chloride with anhydrous aluminum chloride converted them to their respective $AlCl_4^-$ derivatives, **1b** and **1c**. The former showed a 2:1 (cis:trans, refers to 1-Ph *vs.* 3-CH_3) mixture of isomers and the latter a 3:2 mixture (trans:cis 1-CH_3 and 3-CH_3 relationship).

As anticipated, low-temperature chlorination of a cis–trans mixture of 1-chloro-2,2,3,4,4-pentamethylphosphetane (**12**) followed by the addition of $AlCl_3$ gave **1a** which was identical with that prepared through addition of TMP to PCl_3–$AlCl_3$.

The low-temperature chlorination of the *trans*-*tert*-butylphosphetane (**5**) gave only the *trans*-phosphetanium chloride (**6a**), provided that the nmr spectrum of **6a** was taken immediately after chlorination. Similarly, chlorination of a 1:1 cis:trans mixture rendered a 1:1 ratio of **6a**:**6b**. On standing pure **6a** isomerized; for example, after 1.5 hr at 35° a 1:1 composition was observed, and on standing about 1 day a 3:1 (**6b**:**6a**) equilibrium mixture was reached. The same equilibrium ratio prevailed by starting from a 9:1 mixture of **6b**:**6a**. The equilibration could be stopped by adding dry $AlCl_3$.

Isomer Assignments.—The isomer assignments in **1c** have previously been made on the basis of empirical correlations using ^{13}C nmr.[9] The assignment in the *tert*-butylphosphetanium chloride is made on the same basis; for a 3:1 mixture of **6b**:**6a** the ^{13}C nmr spectrum ($CDCl_3$, shifts relative to TMS-^{13}C) gave a peak at δ 47.86 (J_{PCC} = 8.2 Hz) for ring C-3, corresponding to the major component *vs.* 42.68 (J_{PCC} = 11.3 Hz) for the minor isomer. The relative shifts and coupling constants are parallel to those in **1c**.

In compounds **6** and **10** the equilibrium distribution[10] favors the isomer in which the larger group[11] on phosphorus is pseudoequatorial and is cis to the pseudoequatorial 3-CH_3.[7b,12] This is consistent with the base catalyzed equilibration of **13a–c**; in chloroform



13a, R = Ph; R′ = Bz
b, R = Bz; R′ = CH_3
c, R = Ph; R′ = CH_3

(7) (a) S. E. Cremer and B. C. Trivedi, *J. Amer. Chem. Soc.*, **91**, 7200 (1969); (b) M. Haque, *J. Chem. Soc. B*, 934 (1970).

(8) (a) S. E. Cremer, *Chem. Commun.*, 616 (1970); (b) W. Hawes and S. Trippett, *J. Chem. Soc. C*, 1465 (1969).

(9) The relative chemical shifts of C-3 and the J_{PCC} couplings have been diagnostically used to distinguish between cis and trans isomers.[3m]

(10) In cases **10** and **11** it is assumed that the isomer composition of the tetrachloroaluminate salts produced by $AlCl_3$ treatment reflects the composition in the rapidly equilibrated chlorides.

(11) The relative *A* values for the substituents are *t*-Bu > Ph > CH_3 > Cl; see E. L. Eliel, N. L. Allinger, S. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, p 44.

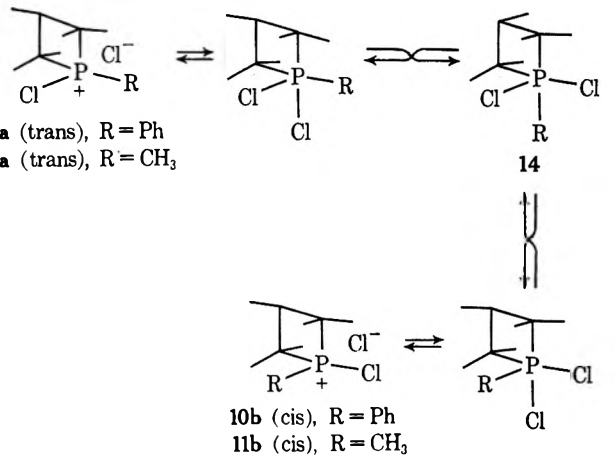
(12) X-Ray data is in accord with placement of the 3-CH_3 in a pseudoequatorial position in 1-phenyl-2,2,3,4,4-pentamethylphosphetane 1-oxide (both cis and trans) and in 1-phenyl-1,2,2,3,4,4-hexamethylphosphetanium bromide, personal communications from M. Haque and L. M. Trefonas; see also M. Haque, *J. Chem. Soc. B*, 117 (1971); M. Haque, *ibid.*, 938 (1970); C. Moret and L. M. Trefonas, *J. Amer. Chem. Soc.*, **91**, 2255 (1969).

or water the predominant isomer (2:1 to 4:1, dependent on R and R′) had the bulkier substituent R cis to the 3-CH_3 group.[13] In compound **11**, however, it is noted that the trans isomer is favored (a 3:2 ratio corresponds to a free energy difference of 0.24 kcal/mol at 25°). Hence, the relative stability of isomers cannot always be predicted on the basis of simple steric considerations, especially when the energy difference is small.

The resultant stereochemistry of the oxides derived from **1b**, **1c**, and **7** on treatment with water provides indirect evidence that the above cis–trans assignments are reasonable (*vide infra*).

Mechanism of Isomerization.—One pathway for isomer interconversion involves a manifold of pentacovalent phosphorus intermediates (Scheme III).

SCHEME III



10a (trans), R = Ph
11a (trans), R = CH_3

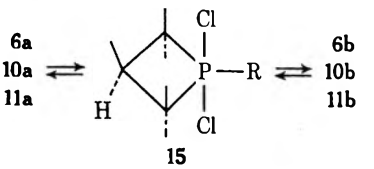
14

10b (cis), R = Ph
11b (cis), R = CH_3

Ample precedent for pseudorotation in similar systems is available.[3a,14] The four-membered ring is best accommodated in the equatorial–apical positions of a trigonal bipyramid because of angle constraint.[3a,15] The intermediate **14**, however, is of high energy, especially if R = *tert*-butyl; the two chlorine atoms are also in the unfavored equatorial positions.[16] A case in point is *cis*- and *trans*-1-*tert*-butyl-1,2,2,3,4,4-hexamethylphosphetanium iodide which do not interconvert on heating with 1 *N* NaOH.[17]

An alternate pathway for stereomutation is shown in Scheme IV; Quin first proposed a similar scheme to explain cis–trans interconversion (rapid on the nmr time scale) in phospholenium salts.[18] The ring spans the two equatorial positions in the trigonal bipyramid **15** (intermediate or transition state); previous stereochemical[3d,19] and nmr data[3g] suggest this geometry especially when other balancing, stereoelectronic factors[16a] are present. In an idealized trigonal bipyramid the two equatorial positions are 120° apart; however, it is possible that the four-membered ring spans these

SCHEME IV



6a **10a** **11a** ⇌ **6b** **10b** **11b**

15

R = CH_3, *t*-Bu, Ph

positions in an unsymmetrical trigonal bipyramid with one of the basal angles <120°. The relative rates (in the nmr at 35°) of interconversion (Ph > CH_3 > *t*-Bu) in **10**, **11**, and **6** are consistent with Scheme IV. An inductive effect (*t*-Bu > CH_3 > Ph) would slow down the rate of Cl^- attack[20] at P^+; moreover, a steric effect may be present in the *t*-Bu derivative.

As a test of Quin's[18] suggestion of rapid interconversion of the isomers of 1-chloro-1,2,5-trimethyl-3-phospholenium chloride (**16**), we have treated this salt with dry $AlCl_3$ in both $CDCl_3$ and nitrobenzene. This froze the equilibration and gave nmr signals for the separate isomers (ratio ~5:1).

It should be noted that the ^{31}P shifts in **6**, **10**, and **11** are virtually identical with their $AlCl_4^-$ derivatives and range from −110 to −138 ppm. Thus, the concentration of pentacovalent intermediates must be small in Scheme III or IV; it is assumed that the ^{31}P values for **14**, **15**, etc., would be at least 0–10 ppm.[20b] Likewise, if **15** is a transition state, the ^{31}P shifts are also understandable.

Water Quench of Intermediates.—Table I summarizes the stereochemical relation of the phosphetane oxides to the salt precursors. The salts in CH_2Cl_2 were quenched with water by two methods: (a) water was added dropwise to a cold solution of the intermediate; (b) the intermediate was added dropwise to cold water. The data for **1b** and **1c** suggest that the latter quenching method gives a mixture of oxides whose

TABLE I

H_2O QUENCH OF THE INTERMEDIATE SALTS

Compound	Isomer ratio[a] of salts (c:t)	Mode of quench	Isomer ratio[a] of oxides (c:t)
1b	2:1	H_2O to salt	1:3
		Salt to H_2O	2:1
1c	7:3	H_2O to salt	1:3
		Salt to H_2O	7:3
	2:3	H_2O to salt	1:4
		Salt to H_2O	3:7
1a		H_2O to salt	>95% trans
		Salt to H_2O	>95% trans
6a	Pure trans	NaOH[b]	Pure trans
6b:**6a**	3:1	NaOH[b]	3:1
16	~5:1[c]	H_2O to salt	~3:2
		Salt to H_2O	~7:1

[a] The ratios are approximate in some cases due to integration of partially overlapping peaks; the error is estimated at ±10%. In the case of **1b** and **1c**, the ratios are the average of three separate runs. [b] The mode of quench was immaterial in this case, since the salt did not react with H_2O in the cold. Sodium hydroxide was used for the conversion—see Discussion and Experimental Section. [c] The ratio obtained by treatment of **16** with $AlCl_3$ is assumed to reflect the ratio in **16**.

(13) B. C. Trivedi, Ph.D. Dissertation, Illinois Institute of Technology, Chicago, Ill., 1970.

(14) S. E. Cremer, R. J. Chorvat, and B. C. Trivedi, *Chem. Commun.*, 769 (1969).

(15) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).

(16) (a) E. L. Muetterties, W. Mahler, and R. Schmutzler, *Inorg. Chem.*, **2**, 613 (1963). (b) The energy barrier associated with placing an alkyl or aryl group in an apical position has been reported: D. Gorenstein, *J. Amer. Chem. Soc.*, **92**, 644 (1970).

(17) S. E. Cremer and C. H. Chang, *Chem. Commun.*, 1156 (1969).

(18) L. D. Quin and T. P. Barket, *J. Amer. Chem. Soc.*, 4303 (1970).

(19) D. J. H. Smith and S. Trippett, *Chem. Commun.*, 855 (1969).

(20) (a) This is consistent with the relative ease of dissociation of a series of phenyl- and chloro-substituted phosphoranes;[20b] (b) D. B. Denney, D. Z. Denney, and B. C. Chang, *J. Amer. Chem. Soc.*, **90**, 6332 (1968).

composition correlates with that of the salts. That is, with an excess of water present a given isomer is rapidly converted to its oxide with retention of configuration about phosphorus.[21] In the reverse mode of quench, in which water is the limiting reagent, chloride ions are formed after the first drop of water has been added; the chloride ion then allows equilibration between the cis and trans tetrachloroaluminate salts. Subsequently, the cis *vs.* trans intermediates are bled off to the oxides at different rates; the predominant isomer is derived from the salt which reacts fastest. Thus either a 7:3 or 2:3 (cis:trans) mixture of **1c** leads to an isomer mixture which contains 75–80% of the trans oxide.[22] To support the assumption that the isomers of **1c** interconvert in the presence of Cl^-, a nonequilibrium composition, 4:1 (cis:trans) was treated with lithium chloride; a 3:2 (cis:trans) ratio was observed shortly after the addition. Trace amounts of water also induced interconversion. When **1c** was heated at 80° in acetonitrile with a trace of water, the equilibrium composition (2:3, cis:trans) was observed; this ratio was identical with that from treatment of **11** with $AlCl_3$.

Since **1a** is not associated with cis–trans isomerism, the mode of quench has no effect on the stereochemical outcome of the acid chloride **3**. It is curious that the reaction gives nearly one pure isomer.[23]

Treatment of **7a** with water by either mode of quench gave unexpected results. Examination of the methylene chloride layer revealed only about one-quarter of the expected amount of oxide; inspection of the aqueous layer showed the presence of a compound whose nmr spectrum was identical with that of **6a**. In a subsequent experiment it was found that solid **6a** (or **6b**) could be dissolved in water and then recovered unchanged after removal of the solvent. The *tert*-butyl substituent apparently makes attack at P^+ quite slow; this same effect was previously noted on the rate of isomerization of **6** by chloride ion.

On heating a sample of **6a** in H_2O at steam bath temperatures it was transformed into pure trans **4a** in about 45 min. Likewise a 9:1 mixture of **6b**:**6a** gave a 3:1 (cis:trans) composition of **4b**:**4a** under identical conditions, but required ~45 hr; a control experiment showed that **4b** does not give **4a** in aqueous HCl at 100° for 56 hr. These results are readily understood if one assumes that the equilibration **6a** ⇄ **6b** is quite slow[24] in water relative to the rate of conversion to oxide. In **6a** the transformation to **4a** is faster than its interconversion to **6b**. However, since the rate of **6b** → **4b** is about 60 times slower, some competitive isomerization occurs, but a predominance of the cis oxide is still obtained. Aqueous sodium hydroxide treatment of **6a** and **6b** gives the respective oxides **4a** and **4b** without concomitant isomerization.

(21) Ample precedent for retention of configuration about phosphorus is available: see ref 2g, 3a,d, and 7a.

(22) In the hydroxide decomposition of other phosphetanium salts, a preference for the trans oxide has been observed.[14]

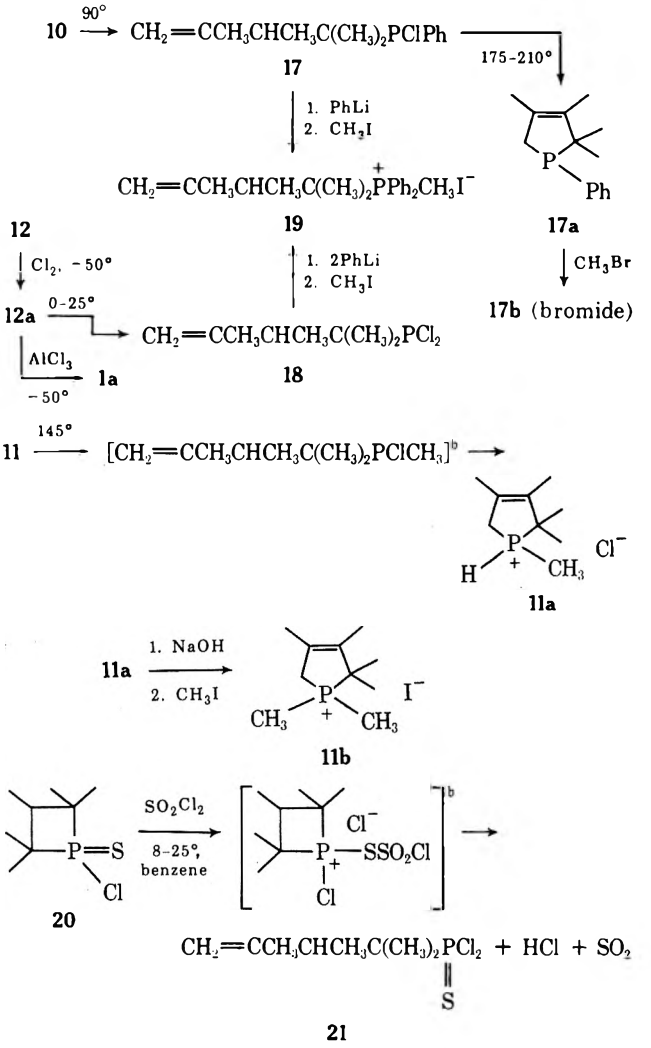
(23) A 2:1 cis:trans mixture of the acid chlorides[7a] in methylene chloride does not change composition when stirred with water (treated with $AlCl_3$) at 0° for 3 hr. Hence, it is assumed that, if the cis isomer had been present, it would have survived in the work-up process.

(24) In studies on isomerization of phosphetanium salts in base,[14] we have qualitatively observed slower stereomutation in H_2O than $CHCl_3$. Increased solvent polarity would stabilize the salts relative to the pentacovalent intermediate. Likewise, **6a** → **6b** and **6b** → **6a** is found to be faster in CH_2Cl_2 than in H_2O.

Quin[18] had earlier observed difficulty in obtaining a reproducible isomeric composition of 1,2-dimethyl-3-phospholene oxide on hydrolysis of the intermediate salt. That the stereochemistry of a similar system is dependent on the mode of quench was shown by hydrolysis of 1,2,5-trimethyl-3-phospholenium chloride (**16**),[18] Table I. The isomer assignments in **16** are tentative; it is assumed that the addition of **16** to H_2O reflects the cis–trans composition at equilibrium. The isomer assignments in 1,2,5-trimethyl-3-phospholene oxide have already been established.[18,25]

Thermal Decomposition of the Phosphetanium Chlorides.—In an attempt to dry (for analysis) the phosphetanium chlorides **10** and **11** at elevated temperatures under vacuum, the salts decomposed. On purification of one of the products, **17**, by distillation, ring closure occurred to give **17a**. Scheme V summarizes the results of these and other reactions, including characterization of liquid products by conversion to crystalline derivatives. During the course

SCHEME V[a]



[a] Structure proof for these compounds is contained in the Experimental Section. [b] The compounds in brackets are postulated, unisolated intermediates.

(25) A. Bond, M. Green, and S. C. Pearson, *J. Chem. Soc. B*, 929 (1968). Total nmr analysis of the phospholene (and oxide) supports the stereochemical assignments; J. P. Albrand and J. B. Robert, personal communication.

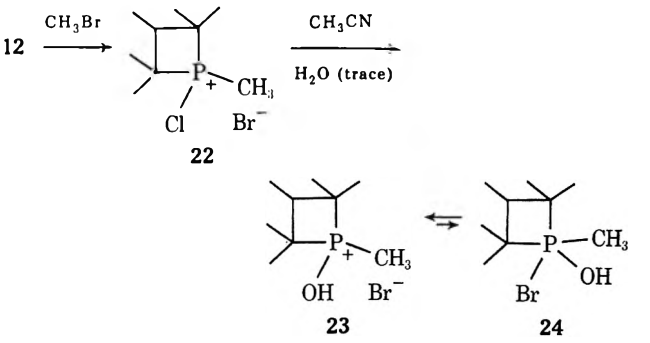
of this work,[26] Trippett[27] reported on the preparation of **17a** and **18** by similar reactions.

The ease of ring opening, **12a** > **10** > **11**, qualitatively parallels the combined electronegativity of the substituents on phosphorus. Phosphetanium salts which only have aryl and/or alkyl groups on phosphorus thermolyze at 200–350°.[28] In comparison, 1-benzyl-1,2,2-trimethylazetidinium perchlorate gives *N*-methyl-*N*-(3-methyl-3-buten-1-yl)benzylamine perchlorate on refluxing for 3 days in acetonitrile.[29]

Conversion of the phosphetanium chlorides to acyclic olefins bears analogy to a prior observation[13] in which **20** was converted to **21** by sulfuryl chloride.[30] In contrast **2a** did not react with sulfuryl chloride; this is reasonable in view of the greater nucleophilicity of sulfur (in P=S) *vs.* oxygen (in P=O).[31] The driving force for the formation of **17**, **18**, and **21** is attributed to angle strain in the four-membered ring.[31]

Hydrogen Bromide Adducts of Phosphetane Oxides.—In an earlier attempt to establish the stereochemistry of **1c**, we tried to convert a known[8a] isomeric mixture (2:1, trans:cis) of **12** with methyl bromide to the respective isomeric salts; isomer interconversion, at that time, had not been anticipated. The quaternization proceeded very slowly to give **22**, mp 176–179°. Recrystallization of this from acetonitrile (which was not rigorously dried) gave a different compound, mp 235–249° dec, which did not contain chlorine. The nmr spectrum and elemental analysis suggested isomeric (2:1) phosphetane oxide–HBr adducts shown as **23**. Treatment of *trans*-**2c** in chloroform or benzene with dry HBr gave a product which was identical with the major isomer of **23**; likewise *cis*-**2c** and HBr yielded the minor isomer. The ^{31}P chemical shifts of these adducts and that derived from **4a** were about 30 ppm downfield from the parent oxide; similar shifts have been reported for acyclic phosphine oxides.[32] The infrared of the HBr addition products showed the absence of P=O stretch (~1150–1200 cm^{-1}) and the presence of several new peaks in the region 1800–2700 (broad, PO–H stretch?) and 920–960 cm^{-1} (strong and broad, PO–H bending?). It was found that cis–trans interconversion of **23** at 100° in tetrachloroethane for 5 days does not occur. Moreover, these adducts are readily sublimed by heating under vacuum without apparent loss of HBr.

From the ^{31}P data it is unlikely that the structure of **23** can be written as **24**; however, an equilibrium, **23** ⇄ **24**, cannot be ruled out, especially if **23** is the predominant species. The absence of isomer interconversion is reasonable since Scheme IV does not apply (apical groups are not identical) and Scheme III would include high energy intermediates (*e.g.*, CH_3 apical,



OH and Br equatorial). Hopefully, a definitive structure will be forthcoming from X-ray studies.[23]

Experimental Section

Nmr spectra were recorded on a Varian A-60A spectrometer; tetramethylsilane was used as an internal standard. In those cases in which H_2O was employed as the solvent, Tier's salt $[(CH_3)_3Si(CH_2)_3SO_3Na \cdot H_2O]$ was the reference standard. The ^{31}P–^1H decoupling experiments were performed with an NMR specialties Model HD-60A heteronuclear spin decoupler. Microanalyses were carried out by Alfred Bernhardt, Mikroanalytisches Laboratorium, Elbach, West Germany. All boiling and melting points (Thomas-Hoover apparatus) are uncorrected. All reactions were conducted under a nitrogen atmosphere; reaction work-up and isolation of moisture sensitive intermediates were conducted in a Labconco glove box in a dry, nitrogen atmosphere. The low temperature for the nmr studies was determined by methanol calibration.[34]

1-Chloro-1-phenyl-2,2,3,4,4-pentamethylphosphetanium Tetrachloroaluminate (1b).—To 40 g (0.30 mol) of anhydrous aluminum chloride (powder) suspended in 100 ml of methylene chloride was added 54 g (0.30 mol) of phenylphosphonous dichloride in 100 ml of methylene chloride. The mixture was briefly stirred until homogeneous and then cooled to 0–5° while 34 g (0.30 mol) of 2,4,4-trimethyl-2-pentene in 100 ml of methylene chloride was added dropwise over 2 hr. The solution was allowed to warm to room temperature and was stirred overnight. The solvent was removed under vacuum (~20 mm) to give a crude, crystalline solid. The nmr spectrum ($CDCl_3$) of the crude product showed two isomers in a 2:1 ratio (estimated due to overlap of peaks). The tetrachloroaluminate was recrystallized twice from hot, dry acetonitrile (minimum) and dry ethyl acetate to give about 50 g of white, crystalline salt, mp 84–104° (sealed tube). The nmr spectrum ($CDCl_3$) of the major component showed peaks at τ 1.73–2.33 (m, 5 H), 6.67–7.20 (m, 1 H), 8.27 (d, 6 H, $J_{PCCH} \approx$ 24 Hz), 8.30 (d, 6 H, J_{PCCH} = 25.5 Hz), 8.80 (d d, 3 H, J_{HCCH} = 7 Hz, $J_{PCCCH} \sim$ 1 Hz). The minor isomer showed peaks at 8.28 (d, 6 H, $J \approx$ 24 Hz), 8.39 (d, 6 H, J = 25.5 Hz), and 8.73 (d d, 3 H, J_{HCCH} = 7 Hz, $J_{PCCCH} \approx$ 1 Hz); the aromatic and ring protons overlapped with those of the major isomer. A moderate concentration of tetrachloroaluminate formed two layers in chloroform. The upper layer contained most of the salt; the lower layer was about tenfold less concentrated in salt. In methylene chloride only one homogeneous phase was apparent. On ^{31}P–^1H decoupling all doublets due to ^{31}P coupling collapsed to singlets. From the frequency used to decouple this sample, the ^{31}P chemical shift was calculated[35] to be -111 ± 2 ppm (relative to 85% H_3PO_4); two standards (trimethyl phosphite and trimethyl phosphate in a sealed capillary tube) were employed as references for the calculation. Use of two references provided an internal check on the reliability of this method; the experimental difference (138 ± 1 ppm) in ^{31}P shift of the standards was in accord with literature values.[6b] This same technique was used for other ^{31}P shifts in this paper.

Anal. Calcd for $C_{14}H_{21}AlCl_5P$: C, 39.51; H, 5.21; Al, 6.34; Cl, 41.66; P, 7.28. Found: C, 39.25; H, 5.49; Al, 6.50; Cl, 41.39; P, 7.43.

(26) The conversion of **10** → **17** and **20** → **21** was first reported at the Third Great Lakes Regional Meeting of the American Chemical Society, Northern Illinois University, DeKalb, Ill., June 5–6, 1969. Credit for the first observation of thermolysis of a phosphetanium chloride is due to M. Green, *Proc. Chem. Soc., London*, 177 (1963).

(27) J. R. Corfield, M. J. P. Harger, R. K. Oram, D. J. H. Smith, and S. Trippett, *Chem. Commun.*, 1350 (1970).

(28) S. E. Cremer and L. Wilkinson, unpublished work.

(29) N. J. Leonard and D. A. Durand, *J. Org. Chem.*, **33**, 1322 (1968).

(30) Sulfuryl chloride converts R_2PSCl to R_2POCl in acyclic systems; R. Cölln and G. Schrader, *Chem. Zentralbl.*, 17390 (1959).

(31) See ref 6a, p 230.

(32) See ref 6b, Chapter 4, pp 284–285.

(33) Several phosphetane–HBr adducts are under study by C. N. Caughlan, Montana State University. An X-ray of triphenylarsenic hydroxybromide [G. Ferguson and E. W. Macaulay, *Chem. Commun.*, 1288 (1968)] is suggestive of a structure $Ph_3As^+—O^{1/2}- \cdots H \cdots Br^{1/2}-$; the bonding in **23** may be similar.

(34) A. L. Van Geet, *Anal. Chem.*, **42**, 679 (1972).

(35) J. B. Stothers and J. R. Robinson, *Can. J. Chem.*, **42**, 967 (1964).

The quench of 1b with H_2O followed the general procedure for that of 1c (*vide infra*). The isomer ratio (Table I) in the oxide was determined (nmr, benzene) by integration of the C-CH_3 groups at the 2 and 4 positions.[2f]

1-Chloro-1,2,2,3,4,4-hexamethylphosphetanium Tetrachloroaluminate (1c).—This intermediate was prepared in 80–90% yield by the general method described for (1b).[2f] An nmr (CH_2Cl_2) spectrum of the crude reaction mixture (prior to evaporation) indicated an isomer ratio or ~4:1 (cis:trans).[36] The nmr spectrum (CH_2Cl_2) of the major component (cis isomer) showed absorption at τ 7.37 (d, 3 H, J_{PCH} = 11 Hz), ~8.41 (d, 6 H, J_{PCCH} ~ 26 Hz), ~8.43 (d, 6 H, J_{PCCH} ~ 24 Hz), 8.88 (d d, 3 H, J_{HCCH} = 7 Hz, J_{PCCCH} = 1 Hz). The minor component showed a peak at τ 7.32 (d, 3 H, J_{PCH} = 11 Hz); the upfield methyl absorption partially overlapped with that of the major component. The elemental combustion analysis and ^{13}C nmr spectrum have been reported.[3m] The cis and trans isomers showed ^{31}P shifts at −126 and −114 ppm, respectively.

Equilibration of the Isomeric Tetrachloroaluminate Salts (1c).—A sample of the salt (cis:trans, 4:1) in dry CH_3CN (dried over Linde Molecular Sieves 3A and then passed through Woelm neutral alumina) was heated in a sealed, degassed nmr tube at about 80°. The isomer ratio gradually changed: ~3:1 (2 hr), ~2:1 (4.5 hr), ~16:9 (7 hr), ~11:9 (11 hr), ~1:1 (19 hr), and ~9:11 (24 hr).

A sample of the salt (initially cis:trans, 4:1) was dissolved in dry acetonitrile and then solid LiCl (dried at 135°) was added to saturate the solution. An nmr spectrum this solution indicated that equilibration had already started (cis:trans, 3:2) at room temperature; heating the sealed, evacuated nmr tube for 1 hr at 80° was sufficient to reach the equilibrium composition (cis:trans, 2:3).

A solution of 8 g of the tetrachloroaluminate salt (cis:trans, 4:1) in 20 ml of dry CH_3CN in a flask was heated to about 80° for 13 hr to give a 3:2 (cis:trans) mixture; then, about 100 mg of D_2O was added; and the reaction was heated for 3 hr to give the equilibrium composition (cis:trans, 2:3).

H_2O Quench of 1c.—To 4.3 g of recrystallized tetrachloroaluminate salt (cis:trans, 2:3) in dry CH_2Cl_2 at 0°, 5 ml of water was added slowly and dropwise (*via* a medicine dropper) over 2 hr with stirring; then an additional 75 ml of water was added over 2 hr at 0°. The layers were separated, and the water layer was extracted three times with an equal volume of $CHCl_3$. The combined organic layers were dried and evaporated to give 2.1 g (95%) of 2c; the isomer ratio 4:1 (trans:cis) was determined by relative integration of the characteristic P-CH_3 groups in the nmr (D_2O) spectrum.

For the reverse mode of quenching, 4.6 g of intermediate (cis:trans, 2:3) in 100 ml of dry CH_2Cl_2 was added dropwise to 80 ml of water (maintained at 0–5° by external cooling) which was rapidly stirred. A nitrogen inlet tube was connected to the pressure equalized addition funnel to prevent water vapor from contacting the CH_2Cl_2 solution prior to its contact with the bulk sample of water. Work-up as described for the addition of H_2O to the tetrachloroaluminate salt gave a 92% yield of oxide, ~3:7 (cis:trans).

General Chlorination Procedure of Phosphetanes.—A solution of chlorine (0.015 mol) was prepared by passing dry chlorine into 10 ml of dry methylene chloride at about −30°; the flask and its contents were weighed to follow the amount of chlorine uptake. The solution was then transferred under nitrogen to an addition funnel and added slowly (15–30 min) to a stirred solution of phosphetane (0.015 mol) in 8 ml of methylene chloride. The temperature was maintained at −60 to −50° by external cooling. The solution was then placed in a drybox in order to fill nmr tubes or to add anhydrous aluminum chloride. The nmr spectra of the chlorinated solutions were "clean" which indicated that chlorination occurred in nearly quantitative yield.

H_2O Quench of 1-*tert*-Butyl-1-chloro-2,2,3,4,4-pentamethylphosphetanium Tetrachloroaluminate (7).—To 7a (prepared from chlorination of 2 g of 5 followed by $AlCl_3$ addition) in 8 ml of dry CH_2Cl_2 at 0°, 8 ml of water was added dropwise over 3 hr. The layers were separated, and the water was extracted three times with 25 ml portions of chloroform. Evaporation of the CH_2Cl_2–$CHCl_3$ gave only ~25% of the expected amount of oxide; the nmr spectrum showed it to be pure trans. The aqueous solution contained the chloride analog of 7a (namely, 6a): the nmr spectrum (H_2O) showed peaks at τ 8.26 (d, 6 H, J_{PCCH} ~ 23 Hz), 8.33 (d, 9 H, J_{PCCH} = 19 Hz), and 8.43 (d, 6 H, J_{PCCH} = 21.5 Hz). The cold, water layer was brought to pH 9–10 with sodium hydroxide and extracted with chloroform. Evaporation of the chloroform and nmr examination of the solid in CH_2Cl_2 showed only trans oxide 4a. The salt 7a was also added slowly to an equal volume of water at 0°; the results were identical with those just described.

Similarly, a 3:1 mixture of 7b:7a was treated with water by both methods of quench. In each case the aqueous layer contained a 3:1 mixture of 6b:6a. Neutralization with sodium hydroxide gave a 3:1 mixture of the 4b:4a. The nmr spectrum (H_2O) due to 6b in a mixture showed peaks at τ 8.23 (d, 6 H, J_{PCCH} = 23.5 Hz), 8.41 (d, 9 H, J_{PCCH} = 19.3 Hz), 8.46 (d, 6 H, J_{PCCH} = 21.8 Hz), and 8.89 (d d 3 H, J_{HCCH} = 7 Hz; overlaps with 6a).

1-Chloro-1,2,2,3,4,4-hexamethylphosphetanium Chloride (11).—Chlorination of either *trans*-1,2,2,3,4,4-hexamethylphosphetane (>95%) or a cis:trans (7:3) mixture of isomers using the general chlorination method gave the same nmr (CH_2Cl_2) pattern: τ 6.4–6.8 (very broad doublet, 3 H, J_{PCH} ~ 13 Hz), 8–8.8 (four broad peaks, 12 H), 8.95 (d d, 3 H, J_{HCCH} = 7 Hz, J_{PCCCH} = 1 Hz). As the sample was cooled from the normal probe temperature ~35° to lower temperatures the upfield methyl absorption (τ 8–8.8) became sharper and the low field doublet (P-CH_3) changed into two doublets. At −20° the major isomer showed peaks at τ 6.5 (d, J_{PCH} = 12.5 Hz), 8.32 (d, J_{PCCH} = 26.5 Hz), 8.59 (d, J_{PCCH} = 23.4 Hz); the minor isomer showed peaks at τ 6.6 (d, J_{PCH} = 12.5 Hz), 8.33 (d, shoulder, J_{PCCH} ~ 26 Hz), 8.48 (d, J_{PCCH} = 23.2 Hz). The C_3-CH_3 protons occurred at τ 8.95 for both isomers. The nmr spectrum reverted to its original pattern when the sample was allowed to warm to 35°. A ^{31}P–^1H decoupling experiment at 35° gave a ^{31}P value of approximately −121 ppm.

Addition of $AlCl_3$ to 11.—Samples of 11 derived from either the *trans*-phosphetane or a cis:trans (7:3) mixture were treated with an equivalent of $AlCl_3$ in CH_2Cl_2 solvent. In each case the nmr spectrum was the same. The ratio of isomers was about 3:2 (trans:cis); the nmr spectrum was also identical with the tetrachloroaluminate salt prepared from methylphosphonous dichloride–aluminum chloride and TMP followed by equilibration of the isomers.

1-Chloro-1-phenyl-2,2,3,4,4-pentamethylphosphetanium Chloride (10).—The general method of chlorination was applied to >95% *trans*-1-phenyl-2,2,3,4,4-pentamethylphosphetane as well as to a cis:trans (7:3) mixture of the phosphetanes. In each case the same product was obtained. Rigorous exclusion of water was required since the phosphetanium chloride is very moisture sensitive. The nmr spectrum (CH_2Cl_2) showed absorption at τ 1.5–2.2 (m, 5 H), 6.6–7.1 (m, 1 H), 8.27 (apparent d, 12 H, J_{PCCH} = 24.5 Hz), 8.78 (d d, 3 H, J_{HCCH} = 7 Hz, J_{PCCCH} = 1 Hz). The ^{31}P shift was −110 ppm. When the anhydrous phosphetanium chloride partially hydrolyzed in the presence of trace amounts of water, additional peaks were observed in the nmr spectrum at τ −4 to −5 (s, function of the degree of hydrolysis), 8.20 (d, J_{PCCH} = 23.8 Hz), and 8.33 (d, J_{PCCH} = 25.8 Hz).

A sample for chlorine analysis was prepared by chlorination of distilled 1-phenylphosphetane; the white solid was washed in the glove box with anhydrous ether and then dried at 25° under vacuum (0.1 mm).

Anal. Calcd for $C_{14}H_{21}Cl_2P$: Cl, 24.35. Found: Cl, 24.74.

A sample of phosphetanium chloride in CH_2Cl_2 was treated with an equivalent of anhydrous $AlCl_3$; the $AlCl_3$ dissolved in this reaction. The nmr spectrum (CH_2Cl_2) showed the presence of two isomers in a ratio of 2:1 (cis:trans); the nmr spectrum (CH_2Cl_2) was identical with that of the phosphetanium tetrachloroaluminate salt prepared from 2,4,4-trimethyl-2-pentene and phenylphosphonous dichloride–aluminum chloride; moreover the chemical shifts and coupling constants in CH_2Cl_2 were similar to those in $CDCl_3$ (*vide supra*).

A low-temperature nmr study was run on 10. As the sample was cooled the original doublet at τ 8.27 broadened at the base line; near 0°, additional peaks were observed which flanked this doublet. At −10 to −20° these peaks became sharp: τ 8.25 (d, J_{PCCH} = 24 Hz) and 8.35 (d, J_{PCCH} = 25.7 Hz). In addition, the upfield absorption at 8.78 changed to two broad doublets (J_{HCCH} ~ 7 Hz for each doublet). The isomer ratio at −20° was about 3:2. The low-temperature spectrum reverted to the original when allowed to warm to 35°.

(36) The initial isomer ratio will sometimes vary and is probably dependent on the amount of water present in the reagents.

1-*tert*-Butyl-2,2,3,4,4-pentamethylphosphetane 1-Oxide (4).—The synthesis of this compound has appeared elsewhere.[3j] The pure trans oxide, mp 149–151°, showed peaks in the nmr spectrum (CH_2Cl_2) at τ 8.0–8.4 (m, 1 H), 8.70 (d, 9 H, J_{PCCH} = 13.5 Hz), 8.73 (d, 6 H, J_{PCCH} = 17 Hz), 8.82 (d, 6 H, J_{PCCH} = 15.2 Hz), 9.15 (d, 3 H, J_{HCCH} = 7 Hz, J_{PCCCH} = 1.5 Hz).

The cis isomer was obtained by sodium hydroxide treatment of a 3:1 (cis:trans) mixture of **7b:7a**. Repeated recrystallization of the predominately cis isomer from cyclohexane followed by fractional sublimation gave a sample, mp 87–90.5°, which was ~90% cis oxide. The nmr spectrum (CH_2Cl_2) showed peaks at τ 7.7–8.1 (m, 1 H), 8.72 (d, 6 H, J_{PCCH} = 16.5 Hz), 8.80 (d, 9 H, J_{PCCH} = 13.5 Hz), 8.86 (d, 6 H, J_{PCCH} = 15.5 Hz), and 9.14 (d d, J_{HCCH} = 7 Hz, J_{PCCCH} = 1.3 Hz).

1-*tert*-Butyl-2,2,3,4,4-pentamethylphosphetane (5).—A solution of 26 g (0.12 mol) of the corresponding trans oxide in 200 ml of benzene was reduced with trichlorosilane–triethylamine by the usual method[2f] to give the phosphetane in 90% yield after distillation of the benzene at atmospheric pressure. Sublimation (~40°, 0.1 mm) gave a white, crystalline product, mp 66–67°. An nmr spectrum (benzene) showed peaks at τ 7.41 (q, 1 H, J_{HCCH} = 7.5 Hz); 8.72 (d, 6 H, J_{PCCH} = 19 Hz); 8.76 (d, 9 H, J_{PCCH} = 11.5 Hz); 8.82 (d, 6 H, J_{PCCH} = 5.5 Hz); 9.31 (d, 3 H, J_{HCCH} = 7.5 Hz). A 1:1 mixture of isomers was obtained by heating the trans isomer at 157°.[37] The nmr spectrum (benzene) of the cis isomer showed a characteristic peak at τ 7.99 (d q, 1 H, J_{HCCH} = 7.5 Hz; J_{PCCH} ~ 3.5 Hz); the ratio of cis:trans isomers was determined from this peak and τ 7.41 from the trans isomer. Treatment of the trans isomer with methyl iodide gave white needles, mp 323–326° dec, from acetonitrile–ethyl acetate.

Anal. Calcd for $C_{13}H_{28}IP$: C, 45.62; H, 8.25. Found: C, 45.57; H, 8.08.

1-Chloro-1-*tert*-butyl-2,2,3,4,4-pentamethylphosphetanium Chloride (6).—A solution of 2.0 g of the trans phosphetane 5 was chlorinated using the general procedure. The solution was transferred while still cold to a drybox. An aliquot was immediately examined in the nmr spectrophotometer. A similar aliquot was immediately treated with anhydrous $AlCl_3$ powder. The $AlCl_3$ rapidly dissolved in the solution; after 1 equiv had been added, the original pale yellow solution became light brown. Additional $AlCl_3$ was insoluble in the methylene chloride solution.

The nmr spectrum (CH_2Cl_2) of the phosphetanium chloride showed only one isomer, **6a**, to be present: τ 6.7–7.1 (m, 1 H), 8.15 (d, 6 H, J_{PCCH} = 23 Hz), 8.24 (d, 9 H, J_{PCCH} = 19 Hz), 8.37 (d, 6 H, J_{PCCH} = 21.5 Hz), and 8.80 (d d, 3 H, J_{HCCH} = 7 Hz, J_{PCCCH} = 1 Hz).

The sample of pure *trans*-phosphetanium chloride showed about 10% of the cis isomer after spinning in the probe (about 35°) for 10–15 min. After 90 min in the probe the cis:trans isomer ratio was about 50:50. On prolonged standing at room temperature (58 hr) the cis:trans ratio was 3:1 which is the equilibrium distribution.

The nmr spectrum (CH_2Cl_2) of the *trans*-phosphetanium tetrachloroaluminate (**7a**) showed peaks at τ 6.8–7.4 (m, 1 H), 8.25 (d, 6 H, J_{PCCH} ~ 23 Hz), 8.30 (d, 9 H, J_{PCCH} = 19 Hz); 8.40 (d, 6 H, J_{PCCH} = 21.5 Hz), 8.84 (d d, 3 H, J_{HCCH} = 7 Hz, J_{PCCCH} = 1 Hz). Examination of this sample after 10 days at room temperature showed only trans isomer.

Chlorination of a 1:1 mixture of the *cis*- and *trans*-phosphetane gave a 1:1 mixture of **6a:6b**; the nmr spectrum was taken immediately after the completion of the reaction. The nmr spectrum (CH_2Cl_2) of the *cis*-phosphetanium chloride (**6b**) showed peaks at τ 6.8–7.3 (d q, 1 H, J_{HCCH} = 7 Hz, J_{PCCH} = 2.5 Hz), 8.10 (d, 6 H, J_{PCCH} = 23.4 Hz), 8.30 (d, 9 H, J_{PCCH} = 19.5 Hz), 8.37 (d, 6 H, J_{PCCH} ~ 21.5 Hz), and 8.85 (d d, 3 H, J_{HCCH} = 7 Hz, J_{PCCCH} = 1 Hz). The *cis*-phosphetanium tetrachloroaluminate (**7b**) had nmr (CH_2Cl_2) absorption at τ 6.8–7.3 (m, 1 H), 8.20 (d, 6 H, J_{PCCH} = 23.5 Hz), 8.38 (d, 9 H, J_{PCCH} = 19 Hz), 8.42 (d, 6 H, J_{PCCH} = 21.5 Hz), and 8.87 (d d, 3 H, J_{HCCH} = 7 Hz, J_{PCCCH} = 1 Hz). The ^{31}P shifts (relative to 85% H_3PO_4) of **6b** and **7b** (both in CH_2Cl_2) were −137 and −138 ppm, respectively.

A sample of the phosphetanium tetrachloroaluminate in CH_2Cl_2 was treated with anhydrous ether to precipitate the solid salt. The solid was redissolved and reprecipitated several times to provide an analytical sample.

Anal. Calcd for $C_{12}H_{25}AlCl_5P$: Cl, 43.81. Found: Cl, 43.32.

(37) S. E. Cremer and C. H. Chang, *Tetrahedron Lett.*, 5799 (1968).

The ^{13}C nmr spectrum ($CDCl_3$) of a 3:1 mixture of **6b:6a** showed peaks at δ 50.69 (J_{PC} = 66.8 Hz, C-2), 47.86 (J_{PCC} = 8.2 Hz, C-3), 17.21 (J_{PCC} < 1 Hz, C-5), 24.93 (J_{PCC} < 1 Hz, C-6), 5.78 (J_{PCCC} = 21.4 Hz, C-7), 50.41 [J_{PC} = 25.1 Hz, $C(CH_3)_3$], 24.93 [J_{PCC} < 1 Hz, $C(CH_3)_3$] for the major isomer. The minor isomer had peaks at δ 42.68 (J_{PCC} = 11.3 Hz, C-3), 19.70 (J_{PCC} = 5.8 Hz, C-5), 23.16 (J_{PCC} ~ 0 Hz, C-6), and 7.13 (J_{PCCC} = 21.4 Hz, C-7); the other peaks overlapped with the major component. The numbering of the carbons follows that in previous manuscripts; the chemical shifts were calculated relative to $(^{13}CH_3)_4Si$, and the instrumental methods were as previously described.[3i,m]

Treatment of 6 with H_2O.—Heating an aqueous solution of 3:1 (**6b:6a**) for 45 min at 100° converted all of the **6a** to **4a**, most of which could be extracted out of solution with several portions of CH_2Cl_2. The resultant aqueous solution of 90% pure **6b** was slowly converted to a mixture of cis:trans oxides (*ca.* 3:1) after 45 hr at 100°. Evaporation (under vacuum) of an aqueous solution of **6b** gave a solid which was redissolved in CH_2Cl_2; the nmr spectrum initially showed a 9:1 ratio of **6b:6a**. On standing for 24 hr, the equilibrium distribution (3:1) was obtained.

A solid sample of a **6b** and **6a** mixture which was isolated from aqueous solution was identical (infrared and nmr) with a sample of **6b** and **6a** which had never been in contact with water. For the infrared spectrum (Nujol mull) the samples were dried at 70° under vacuum to remove either H_2O or CH_2Cl_2 which form a solvate with **6**.

Chlorination of 1-Chloro-2,2,3,4,4-pentamethylphosphetane (12) and Conversion to 18.—To 1.0 g (5.7 mmol) of 1-chloro-2,2,3,4,4-pentamethylphosphetane[3m] in 10 ml of dry methylene chloride was added 0.40 g (5.7 mmol) of chlorine in 10 ml of dry methylene chloride; the temperature was maintained below −50° by external cooling. The addition required 5 min; a white precipitate was observed as the chlorine was added. Then 1.2 g (9.0 mmol) of anhydrous $AlCl_3$ was added at −50° and the reaction mixture allowed to warm to room temperature. The resultant solution showed the following absorption in the nmr spectrum: τ 7.02 (m, 1 H), 8.28 (d, 6 H, J_{PCCH} = 32 Hz), 8.30 (d, 6 H, J_{PCCH} = 32.5 Hz), 8.73 (d, 3 H, J_{HCCH} = 7 Hz). The nmr spectrum was identical with that of the tetrachloroaluminate salt **1a** prepared by treatment of TMP with PCl_3–$AlCl_3$.

In a second experiment, 2.0 g of the chlorophosphetane was treated with 0.8 g of Cl_2 in CH_2Cl_2 at −50°. The mixture was allowed to warm to room temperature; after stirring for about 1 hr all of the suspended, white solid went into solution. The nmr spectrum of the solution was consistent with ring-opened product, **18**: τ 5.0–5.3 (m, 2 H), 7.5 (m, 1 H), 8.4 (m, 3 H), 8.87 (d, 3 H, J_{PCCH} = 10.5 Hz), 8.92 (d, 3 H, J_{PCCH} = 13 Hz), 9.03 (d d, 3 H, J_{HCCH} = 7 Hz). Treatment of **18** with phenyllithium and then methyl iodide converted it into its corresponding phosphonium salt which was identical (infrared and nmr) with **19** (*vide infra*).

1-Chloro-1,2,5-trimethyl-3-phospholenium Tetrachloroaluminate.—A sample of the chloride **16** was prepared according to the procedure of Quin;[18] the nmr ($CDCl_3$) values were in agreement with those reported. To 497 mg of the chloride in ~3 ml of $CDCl_3$, 330 mg of anhydrous aluminum chloride was added; all of the $AlCl_3$ went into solution. An additional 50 mg of $AlCl_3$ was added whereupon the light, pale yellow solution turned yellow-brown. The nmr spectrum ($CDCl_3$) of the predominant isomer showed peaks at τ 3.80 (d, 2 H, J_{PCCH} = 35.5 Hz), 6.12 (m, 2 H), 7.30 (d, 3 H, J_{PCH} = 12.8 Hz), and 8.45 (d d, 6 H, J_{PCCH} = 21.5 Hz, J_{HCCH} = 7.3 Hz). The minor isomer showed peaks at τ 3.77 (d, J_{PCCH} = 35.5 Hz, partially obscured by the major isomer) and 7.41 (d, J_{PCH} = 12.5 Hz); the upfield methyl groups were partially obscured by the major isomer and appeared as shoulders. The isomer ratio was ~5:1.

The phospholenium chloride as a suspension in dry nitrobenzene was also treated with a slight excess of $AlCl_3$ whereupon the salt and $AlCl_3$ went into solution. The upfield C–CH_3 doublets of the minor isomer were now distinguishable from the major isomer.

H_2O Quench of 16.—To 3.5 g of the phospholenium salt in 50 ml of CH_2Cl_2 at 0°, 10 ml of water was added slowly. The water layer was saturated with NaCl and extracted repeatedly with CH_2Cl_2. Evaporation of the organic solvent gave 2.4 g 95% yield, of crude product. An nmr spectrum (benzene) indicated an isomer ratio of about 3:2 (cis:trans). The slow addition of 6.0 g of the salt in 50 ml of CH_2Cl_2 to an equal volume of ice water gave 4.2 g, 97% yield, of oxide. The isomer ratio

was ~7:1 (cis:trans).[18,25] The nmr spectrum (benzene) of the cis isomer showed peaks at τ 4.59 (d, 2 H, J_{PCCH} = 23.7 Hz), 7.27 (2 H, six-line pattern, J_{HCCH} = 7 Hz, J_{PCH} = 13 Hz), 8.87 (d, 3 H, J_{PCH} = 12 Hz), and 9.02 (d d, 6 H, J_{HCCH} = 7Hz, J_{PCCH} = 16 Hz). The trans isomer showed peaks at 4.40 (d, 2 H, J_{PCCH} = 26.5 Hz), 7.82 (2 H, apparent five-line pattern, J_{HCCH} = 7 Hz, J_{PCH} = 7 Hz), 8.72 (d, J_{PCH} ~ 12 Hz); the C-CH_3 groups were obscured by the cis isomer.

Thermal Decomposition of 1-Chloro-1-phenyl-2,2,3,4,4-pentamethylphosphetanium Chloride (10) to Chlorophenyl(1,1,2,3-tetramethyl-3-butenyl)phosphine (17).—A fresh sample of the salt **10** in a molecular still was heated at about 90° under vacuum (0.1 mm). A clear colorless liquid, bp 135–137° (1.6 mm), was obtained in 60% yield. The infrared spectrum (neat) showed absorption at 895 cm^{-1} (>C=CH_2) and at 695 and 742 cm^{-1} (monosubstituted phenyl). The nmr spectrum (neat) gave peaks at τ 2.2–3.0 (5 H, aromatic), 5.00–5.38 (2 H, m), 7.20–7.85 (1 H, m), 8.22 (3 H, m), and 8.7–9.4 (9 H, m); the ^{31}P decoupled spectrum was consistent with the assigned structure.

Anal. Calcd for $C_{14}H_{20}ClP$: C, 66.01; H, 7.91; Cl, 13.92; P, 12.16. Found: C, 65.52; H, 8.29; Cl, 14.05; P, 11.95.

The liquid phosphine **17** was characterized by conversion to a solid derivative. To 2g of the chlorophenylphosphine in 25 ml of ether at −30°, 12 ml of phenyllithium (0.7 *M*) was added. The mixture was then stirred at room temperature overnight. Water was added and the ether layer was dried and treated with an excess of methyl iodide. The resultant solid, **19**, was recrystallized twice from acetonitrile–ethyl acetate to give 1.7 g (50% yield), of salt, mp 181–188° dec. The nmr spectrum ($CDCl_3$) showed absorption at τ 1.6–2.4 (10 H, m), 5.0–5.47 (2 H, apparent doublet), 7.07 (d, 3 H, J_{PCH} = 12 Hz), 8.30 (3 H, broad s), 8.40 (d, 3 H, J_{PCCH} = 18 Hz), 8.46 (d, 3 H, J_{PCCH} ~ 20 Hz), 8.94 (d, 3 H, J_{HCCH} = 7 Hz); the single tertiary, allylic hydrogen was obscured by the doublet at τ 7.07.

Anal. Calcd for $C_{21}H_{28}IP$: C, 57.54; H, 6.44; I, 28.95; P, 7.07. Found: C, 57.53; H, 6.50; I, 29.12; P, 6.99.

1-Phenyl-2,2,3,4-tetramethyl-3-phospholene (17a).—The chlorophenylphosphine **17**, 7.7 g, was gradually heated and stirred under a nitrogen atmosphere. At about 175° a slow evolution of HCl gas was observed; at 200–210° the evolution was more vigorous. The liquid was heated at the latter range for 4 hr. On cooling two layers were observed, a viscous upper layer and a smaller bottom layer (about 1.5 g) which was hard. An nmr spectrum (neat) of the upper layer showed peaks at τ 2–3 (m, 5 H), 6.8–7.0 (m, 2 H), 8.28 (broad s, 3 H), 8.53 (broad s, 3 H), 8.77 (d, 3 H, J_{PCCH} = 20 Hz), and 9.28 (d, 3 H, J_{PCCH} = 9 Hz). The upper layer was dissolved in ether and treated with an excess of methyl bromide. The resultant precipitate, 6.9 g, was recrystallized from acetonitrile–ethyl acetate to give 5.3 g of the phospholenium salt **17b**, mp 159–161.5°. The nmr spectrum ($CDCl_3$) of the salt showed peaks at τ 1.6–2.5 (m, 5 H), 5.6–6.6 (m, 2 H), 7.2 (d, 3 H, J_{PCH} = 14 Hz), 8.0 (broad s, 3 H), 8.28 (broad s, 3 H), 8.39 (d, 3 H, J_{PCCH} = 17 Hz), and 8.86 (d, 3 H, J_{PCCH} = 17.5 Hz).

Anal. Calcd for $C_{15}H_{22}BrP$: C, 57.53; H, 7.08; Br, 25.51. Found: C, 57.51; H, 6.79; Br, 25.52.

Thermolysis of 1-Chloro-1,2,2,3,4,4-hexamethylphosphetanium Chloride (11).—The phosphetanium chloride did not show decomposition when dissolved in dry CH_2Cl_2 or $CHCl_3$ and heated at reflux for 24 hr. A 1-g sample was heated to 145° in a sublimation apparatus under vacuum (0.1 mm); a white solid (**11a**) gradually sublimed onto the cold finger. The solid had a distinct phosphine odor and was insoluble in dry benzene. The nmr spectrum ($CDCl_3$) showed resonances at τ 6.3–7.4 (m, 2 H), 7.78 (d, 3 H, J_{PCH} = 15.2 Hz), ~8.37 (broad s, 3 H), ~8.51 (d, 3 H, J_{PCCH} ~ 18 Hz), ~8.55 (broad s, 3 H), and ~8.64 (d, 3 H, J_{PCCH} ~ 16 Hz). The solid was treated with cold 10% NaOH and the liberated phosphine extracted with ether. The ether was dried and treated with methyl iodide to give the methiodide salt **11b**, mp 314–317° dec, and previous darkening at ~290°. The nmr spectrum (CF_3CO_2H) showed peaks at τ 6.88 (broad d, 2 H), 7.98 (6 H, d, J_{PCH} = 14 Hz), 8.14 (broad s), 8.24 (broad s), 8.58 (d, 6 H, J_{PCCH} = 17 Hz).

Anal. Calcd for $C_{10}H_{20}IP$: C, 40.28; H, 6.77; I, 42.57; P, 10.39. Found: C, 40.25, H, 6.56; I, 42.64; P, 10.25.

1,1,2,3-Tetramethyl-3-butenylthiophosphonyl Dichloride (21).—To 9.1 g (0.04 mol) of the sulfide **20**[3m] in 100 ml of benzene, 6.7 g (0.05 mol) of sulfuryl chloride in 50 ml of benzene was added over 20 min; the temperature was kept near 8° by ice bath cooling; considerable gas evolved on warming to room temperature. The mixture, which contained two phases, was stirred at ambient temperature for 24 hr. The solvent was evaporated and the product distilled to give 8.7 g of clear liquid, bp 67–68° (0.1 mm). The nmr spectrum ($CDCl_3$) showed absorption at τ 5.01 (m, 2 H, vinyl protons), 6.83 (six peaks observed, 1 H, J_{HCCH} = 7 Hz, J_{PCCH} ~ 14 Hz), 8.18 (m, 3 H, allylic CH_3), 8.49 (d, 3 H, J_{PCCH} ~ 28 Hz), 8.53 (d, 3 H, J_{PCCH} = 28 Hz), 8.68 (d, 3 H, J_{HCCH} = 7 Hz). A ^{31}P–^1H decoupling experiment was consistent with these assignments.

Anal. Calcd for $C_8H_{15}Cl_2PS$: C, 39.19; H, 6.17; P, 12.63; Cl, 28.92. Found: C, 39.23; H, 6.23; P, 12.49; Cl, 28.95.

1-Chloro-1,2,2,3,4,4-hexamethylphosphetanium Bromide (22) and Its Reaction with H_2O.—To 8 g of 1-chloro-2,2,3,4,4-pentamethylphosphetane (**12**) In 50 ml of dry ether in a thick-walled flask, an excess of methyl bromide was added; the flask was stoppered and allowed to stand at room temperature for 2 weeks. A white precipitate formed very slowly during this period. The solution was then filtered in the drybox to give 2.5 g of the phosphetanium bromide **22**. The filtrate contained unreacted **12**.

The phosphetanium bromide was nearly insoluble in $CHCl_3$ and CH_3CN. It was purified by trituration with hot CH_3CN to give a white solid, mp 176–179° dec (sealed tube under nitrogen). The ^{31}P shift (dilute solution in $CHCl_3$) was −116 ppm. The ^1H nmr spectrum (dilute CH_2Cl_2) showed peaks at τ 6.65 (broad d, 3 H, J_{PCH} = 11 Hz), 8.31 (broad d, J_{PCCH} ~ 25 Hz), 8.40 (d, J_{PCCH} ~ 21.5 Hz), 8.52 (d, J_{PCCH} = 21.5 Hz), 8.90 (3 H, d, J_{HCCH} = 7 Hz).

Anal. Calcd for $C_9H_{19}BrClP$: C, 39.51; H, 7.00; Br, 29.21; Cl, 12.96; P, 11.32. Found: C, 39.52; H, 7.03; Br, 29.06; Cl, 12.67; P, 11.34.

Treatment of **22** with acetonitrile which had not been completely dried, followed by evaporation of the solvent gave white crystals, mp 235–249° dec. Traces of water added to a suspension of **22** in $CHCl_3$ led to the same product, **23**. Addition of excess H_2O or base to **22** gave **2c**, cis and trans. Compound **23** is soluble in $CHCl_3$ and can be sublimed at about 70° (0.1 mm). The nmr spectrum ($CDCl_3$) showed two isomers to be present.

The major component (trans) absorbed at τ −1.87 (s, 1 H), 7.82 (d, 3 H, J_{PCH} = 12.2 Hz), 8.57 (d, 6 H, J_{PCCH} = 18.0 Hz), 8.63 (d, 6 H, J_{PCCH} = 21.3 Hz), and 8.98 (d d, 3 H, J_{HCCH} = 7 Hz, J_{PCCCH} ~ 1 Hz). The minor component (cis) overlapped with the major isomer except for peaks at τ 8.52 (d, 6 H, J_{PCCH} = 18 Hz) and 8.67 (d, 6 H, J_{PCCH} = 22 Hz). The ratio of isomers was ~2:1 (trans:cis).

Anal. Calcd for $C_9H_{20}OBrP$: C, 42.36; H, 7.90; Br, 31.32; P, 12.14. Found: C, 42.53; H, 7.89; Br, 31.20; P, 12.12; Cl, 00.00.

1,2,2,3,4,4-Hexamethylphosphetane 1-Oxide HBr Adduct (23).—To 0.5 g of *trans*-1,2,2,3,4,4-hexamethylphosphetane 1-oxide in 5 ml of $CDCl_3$ a slow stream dry HBr gas was added for several minutes. An nmr spectrum matched the major isomer derived from the addition of H_2O to **22**. The solvent was evaporated and the product recrystallized from dry acetonitrile (sparingly soluble), mp 237–249° dec. The infrared spectrum (Nujol mull) showed strong peaks at 1800–2500 (broad), 990, 895, and 795 cm^{-1}.

The ^{31}P shift (in $CDCl_3$) of the *trans*-phosphetane 1-oxide was −63 ppm and its corresponding HBr adduct was −94.5 ppm.

Similarly, a 7:3 mixture (cis:trans) of oxides was converted to the respective adducts **23**. The cis isomer was identical (nmr) with the minor component derived from addition of H_2O to **22**.

Heating either isomer of **23** for 5 days at 100° in tetrachloroethane in sealed nmr tubes showed no isomer interconversion.

1-*tert*-Butyl-2,2,3,4,4-pentamethylphosphetane 1-Oxide HBr adduct.—Into 5 g of **4a** in 25 ml of dry benzene, a slow stream of HBr gas was bubbled. The solvent was evaporated to give 6.7 g of white solid, mp 158–166°. The product was sublimed (80°, 0.1 mm) and recrystallized twice from dry acetonitrile. The infrared spectrum (Nujol mull) showed absorption at 2700–1800 (broad), 960, 810, 755, and 680 cm^{-1}. The nmr spectrum ($CDCl_3$) exhibited peaks at τ −2.38 (s, 1 H), 7.36–7.87 (m, 1 H), 8.41 (d, 9 H, J_{PCCH} = 15.5 Hz), 8.42 (d, 6 H, J_{PCCH} = 19 H*), 8.47 (d, 6 H, J_{PCCH} = 17 H*), 8.92 (dd, 3 H, J_{HCCH} = 7 H*, J_{PCCH} = 1.5 H*). The ^{31}P shift (in $CDCl_3$) for **4a** was −72 ppm and the HBr adduct, −103 ppm.

Anal. Calcd for $C_{12}H_{26}OBrP$: C, 48.49; H, 8.82; Br, 26.89; P, 10.42. Found: C, 48.58; H, 8.93; Br, 27.11; P, 10.31.

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Registry No.—**1a**, 40084-63-7; *cis*-**1b**, 40084-64-8; *trans*-**1b**, 40084-65-9; *cis*-**1c**, 35616-95-6; *trans*-**1c**, 35616-97-8; **4a**, 35624-08-9; **4b**, 35624-09-0; **5**, 40085-35-6; **5** cis isomer, 22434-52-2; **5** methiodide, 26339-55-9; **6a**, 39990-53-9; **6b**, 39990-54-0; **6** phosphorane form, 39981-51-6; **7a**, 40084-68-2; **7b**, 40084-69-3; **10a**, 39990-55-1; **10b**, 39990-56-2; **10** phosphorane form, 39981-52-7; **11a**, 39990-57-3; **11b**, 39990-58-4; **11** phosphorane form, 39981-53-9; *cis*-**12**, 25145-23-7; *trans*-**12**, 25145-24-8; *cis*-**16**, 39990-60-8; *trans*-**16**, 39990-63-1; **16** phosphorane form, 20699-83-6; *cis*-**16** $AlCl_4$ derivative, 40084-70-6; *trans*-**16** oxide, 35623-32-6; **17**, 30092-42-3; **17a**, 30092-44-5; **17b**, 39981-57-2; **18**, 36044-91-4; **19**, 39981-59-4; **20**, 39981-60-7; **21**, 39981-61-8; **22**, 39990-66-4; **22** phosphorane form, 39981-62-9; *cis*-**23**, 39990-67-5; *trans*-**23**, 39990-68-6; **24**, 39981-63-0; phenyl phosphonous dichloride, 644-97-3; *cis*-1,2,2,3,4,4-hexamethylphosphetane, 35622-00-5; *trans*-1,2,2,3,4,4-hexamethylphosphetane, 35621-97-7; *cis*-1-phenyl-2,2,3,4,4-pentamethylphosphetane, 22434-51-1; *trans*-1-phenyl-2,2,3,4,4-pentamethylphosphetane, 16083-95-7; 1-*tert*-butyl-2,2,3,4,4-pentamethylphosphetane 1-oxide HBr adduct, charged form, 40088-36-6; 1-*tert*-butyl-2,2,3,-4,4-pentamethylphosphetane 1-oxide HBr adduct, neutral form, 9981-10-0.

Stable Carbocations. CLI.[1] Protonation of Cyclic Carboxylic Acid Anhydrides in FSO_3H–SbF_5 ("Magic Acid")–SO_2 Solution

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Protonation of a series of cyclic carboxylic acid anhydrides (**1**–**16**) in SO_2 solutions containing varying amounts of 1:1 mol/mol FSO_3H–SbF_5 was studied by nmr spectroscopy. O-Protonated cyclic carboxylic acid anhydrides formed undergo rapid intermolecular hydrogen exchange with the acid solvent system or excess anhydride, even at the lowest accessible temperatures. Unsaturated cyclic carboxylic acid anhydrides (**1**–**3**), as well as cyclic aromatic carboxylic acid anhydrides (**4**–**10**), were not cleaved in magic acid solution up to 0°, in sharp contrast to the behavior of acyclic saturated cyclic carboxylic acid anhydrides.

Protonation of acyclic carboxylic acid anhydrides in superacids has been studied in our preceding work.[2] A preliminary study of protonation of cyclic anhydrides, including succinic and glutaric anhydrides, was also carried out in FSO_3H–SbF_5–SO_2 solution.[3,4] Protonated cyclic anhydrides such as succinic and glutaric anhydrides could not be observed even when the solutions were prepared and examined at −80°, as they were cleaved in "magic acid" giving the corresponding alkyleneoxocarbenium–carboxonium ions, $^+OC(CH_2)_n$-$COOH_2^+$ (n = 2 and 3, respectively).[5] On the other hand, succinic anhydride was reported to be only partially protonated in sulfuric acid.[6]

In continuation of our studies, we presently wish to report the results of protonation of a series of cyclic (both aliphatic and aromatic) carboxylic acid anhydrides (**1**–**16**) in SO_2 solutions containing varying amounts of 1:1 mol/mol FSO_3H–SbF_5.

Results and Discussion

The chemical behavior of cyclic carboxylic acid anhydrides in FSO_3H–SbF_5–SO_2 is different from that of acyclic anhydrides. In particular cyclic aromatic anhydrides **4**–**10** are not cleaved even with large excess of FSO_3H in SO_2 solution at 0°. They are protonated in the superacid and undergo rapid intermolecular hydrogen exchange with the solvent system. Intramolecular hydrogen exchange seems to be less feasible since the position of the two carbonyl groups are rigidly fixed and consequently their distance is too large. Intermolecular hydrogen exchange processes must be extremely rapid, since static mono- or diprotonated cyclic anhydrides were not observed even at the lowest possible temperature (*ca.* −90°) under the experimental conditions. Consequently, the proton chemical shifts of protonated cyclic anhydrides are dependent upon the concentration of both substrate and superacid used. Pmr parameters of cyclic carboxylic acid anhydrides protonated in SO_2 solutions containing varying amounts of magic acid and their precursors (in SO_2) are summarized in Table I (also showing the proportions of superacid and anhydride in the system).

Unsaturated cyclic carboxylic acid anhydrides including maleic (**1**), dimethylmaleic (**2**), and 3,4,5,6-tetrahydrophthalic anhydride (**3**) show similar behavior in FSO_3H–SbF_2–SO_2 solutions. When **maleic anhydride** (**1**) was protonated with 0.5 equimolar magic acid in SO_2 solution, the pmr absorption of the two vinylic protons was deshielded from δ 6.83 (s) to 7.21 (s). A very deshielded pmr singlet absorption (~0.5 proton intensity) is found at δ 14.5 and is assigned to the OH proton of protonated maleic anhydride, which undergoes intermolecular hydrogen exchange with **1**. The pmr singlet absorption of the two vinylic protons in protonated maleic anhydride **1a** was further deshielded at δ 7.63 when equimolar magic acid was used. The OH proton was slightly shielded to δ 13.5. These data suggest that another intermolecular H exchange process may occur (eq 1). When **1** was treated with a large excess of 1:1 mol/mol FSO_3H–SbF_5 in SO_2 or with neat magic acid solution, the pmr spectra of the resulting solution showed two more deshielded singlets at δ 8.09 and 8.30, respectively. The OH proton is not observed

(1) Part CL: G. A. Olah, G. Liang, G. D. Mateescu, and J. L. Riemenschneider, *J. Amer. Chem. Soc.*, in press.

(2) G. A. Olah, K. Dunne, Y. K. Mo, and P. Szilagyi, *J. Amer. Chem. Soc.*, **94**, 4200 (1972).

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

(4) G. A. Olah, A. M. White, and D. H. O'Brien, *Chem. Rev.*, **70**, 561 (1970).

(5) For a discussion of the general concept of carbocations and differentiation of trivalent carbenium ion from penta- (or tetra-) coordinated carbonium ions, see G. A. Olah, *J. Amer. Chem. Soc.*, **94**, 808 (1972).

(6) R. J. Gillespie and J. A. Leisten, *Quart. Rev., Chem. Soc.*, **8**, 40 (1954).

TABLE I

PMR PARAMETERS OF CYCLIC CARBOXYLIC ACID ANHYDRIDES IN SO_2 SOLUTIONS CONTAINING VARYING MOLAR AMOUNTS OF 1:1 MOL/MOL FSO_3H–SbF_5[a]

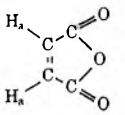
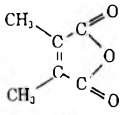
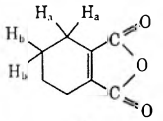
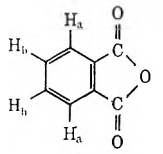
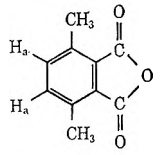
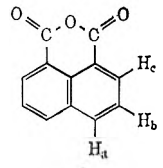
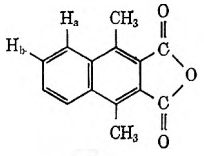
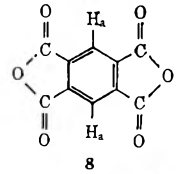
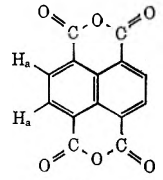
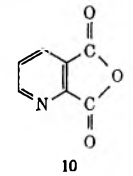
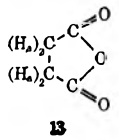
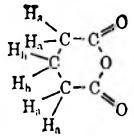
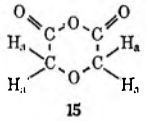
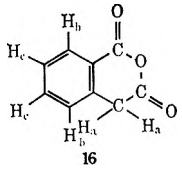
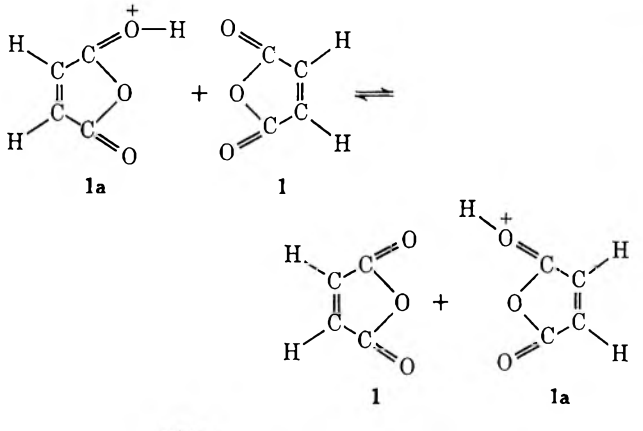
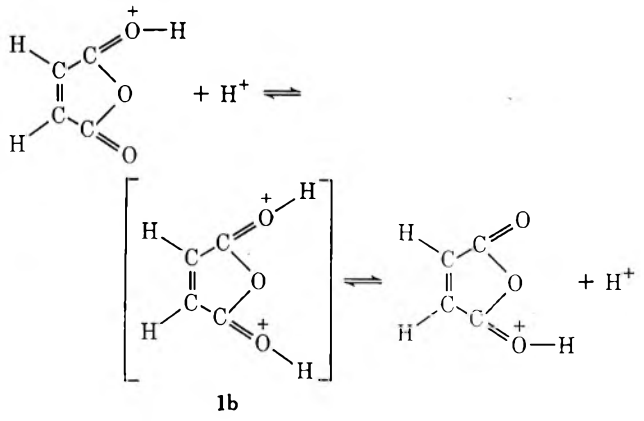
Cyclic carboxylic acid anhydride	Solvent[b] system	δ_{H_a}	δ_{H_b}	δ_{H_c}	δ_{CH_3}	Other
 1	SO_2	6.83 (s)				
	0.5 *M* MA	7.21 (s)				14.5 (OH)
	1.0 *M* MA	7.63 (s)				13.5 (OH)
	Excess MA	8.09 (s)				*c*
	Neat MA	8.30 (s)				*c*
 2	SO_2				1.88 (s)	
	0.5 *M* MA				1.97 (s)	14.0 (OH)
	1.0 *M* MA				2.11 (s)	13.2 (OH)
	Excess MA				2.42 (s)	*c*
	Neat MA				2.90 (s)	*c*
 3	SO_2	2.18 (m)	1.50 (m)			
	0.5 *M* MA	2.36 (m)	1.71 (m)			14.6 (OH)
	1.0 *M* MA	2.70 (m)	1.90 (m)			12.9 (OH)
	Excess MA	2.80 (m)	2.10 (m)			*c*
	Neat MA	3.10 (m)	2.40 (m)			*c*
 4	SO_2	7.73 (s)	7.73 (s)			
	1.0 *M* MA	8.03 (s)	8.03 (s)			14.0 (s, br, OH)
	2.0 *M* MA	8.35 (m)	8.35 (m)			*c*
	4.0 *M* MA	8.50 (m)	8.50 (m)			*c*
	Excess MA	9.38 (m)	9.03 (m)			*c*
	Neat MA	9.80 (m)	9.45 (m)			*c*
 5	SO_2	7.30 (s)			2.25 (s)	
	1.0 *M* MA	8.00 (s)			2.75 (s)	14.5 (OH)
	Excess MA	8.18 (s)			2.90 (s)	*c*
	Neat MA	8.93 (s)			3.70 (s)	*c*
 6	SO_2	9.2 (m)	7.6 (m)	9.2 (m)		
	Excess MA	9.70 (d, 8)	8.68 (t, 8)	9.85 (d, 8)		*c*
	Neat MA	10.3 (d, 8)	9.31 (t, 8)	10.3 (d, 8)		*c*
 7	*d*					
	Excess MA	8.9 (m)	8.3 (m)		3.3 (s)	*c*
	Neat MA	9.3 (m)	9.3 (m)		4.0 (s)	*c*
 8	SO_2	8.42 (s)				
	1.0 *M* MA	9.55 (s)				14.5 (OH, s, br)
	Excess MA	9.73 (s)				*c*
 9	*d*					
	Excess MA	9.50 (s)				*c*
	Neat MA	10.61 (s)				*c*
 10	SO_2	8.20 (dd, 8, 2)	7.73 (dd, 8, 4)	8.83 (dd, 4, 2)		
	Excess MA	9.3 (m)	8.7 (m)	9.3 (m)		9.7 (s, br, NH)
						c

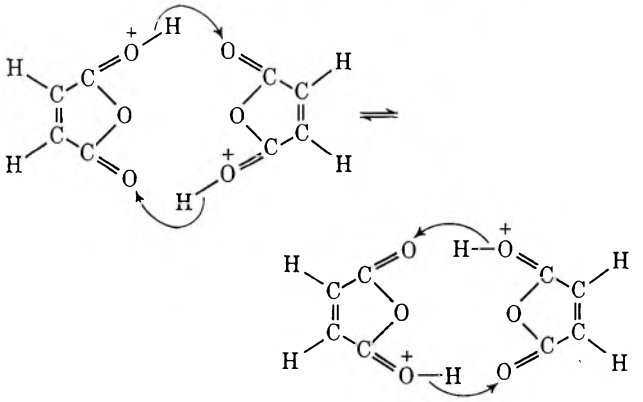
TABLE I (*Continued*)

Cyclic carboxylic acid anhydride	Solvent[b] system	δ_{H_a}	δ_{H_b}	δ_{H_c}	δ_{CH_3}	Other
 13	SO_2	2.73 (s)				
	0.25 *M* MA	2.90 (s)				14.8 (OH, s, br)
	1.0 *M* MA	3.00 (s)				13.2 (OH, s, br)
	3.0 *M* MA	3.80 (s)				c
	4.0 *M* MA	4.60 (s, br)				*c*
	Excess MA[e]	4.47, 5.15				14.43 (OH)
	Wet MA[f]	4.08 (s)				13.6 (s, br)
	Neat MA[g]	5.10 (s)				
 14	SO_2	2.53 (t, 6)	1.80 (qu, 6)			
	1.0 *M* MA	2.68 (t, 6)	2.00 (qu, 6)			16.1 (OH, s, br)
	Wet MA[f]	3.85 (t, 6)	2.80 (qu, 6)			12.7 (OH, s)
	Excess MA[e]	4.40 (t, 6)	3.11 (qu, 6)			13.0 (OH, s)
	Neat MA[g]	5.20 (t, 6)	4.10 (qu, 6)			
 15	SO_2	4.20 (s)				
	0.5 *M* MA	4.30 (s)				13.0 (OH, s, br)
	1.0 *M* MA	4.40 (s)				12.8 (OH, s, br)
	Excess MA[e]	5.58 (s)				13.3 (OH, s, br)
		6.58 (s)				
	Wet MA[f]	5.40 (s)				13.2 (OH, s, br)
 16	SO_2	3.90 (s)	7.5 (m)	7.5 (m)		
	1.0 *M* MA	4.10 (s)	8.0 (m)	7.5 (m)		12.3 (OH, s, br)
	Excess MA[e]	4.91 (s)	8.0-9.0 (m)			13.1 (OH, s, br)
		5.03 (s)	8.0-9.0 (m)			13.3 (OH, s, br)
	Neat MA[g]	5.50 (s)	8.80 (t, 6)	9.60 (d, 6)		
				9.32 (d, 6)		

[a] Proton chemical shifts are reported in parts per million (δ) from external (capillary) TMS. Abbreviation: s, singlet; d, doublet; t, triplet; qu, quintet; m, multiplet; br, broad. The coupling constants are shown in parentheses. [b] Used equimolar amount of magic acid (MA) in SO_2: excess, more than 5 mol equiv of magic acid; wet, excess magic acid containing 10% water; neat, neat magic acid at room temperature. [c] The OH protons are not observable because of rapid intermolecular hydrogen with the solvent system. [d] Insoluble in SO_2. [e] Formation of oxocarbenium-carboxonium ions. [f] Formation of diprotonated dicarboxylic acids. [g] Formation of dioxocarbenium ions.







since it now rapidly exchanges with the superacid system. It is suggested that under these conditions diprotonated maleic anhydride **1b** may be involved in the intermolecular exchange process. The deshielding of the vinylic protons is proportional to the molar concentration of magic acid used.

Dimethylmaleic anhydride (2)[7] **and 3,4,5,6-tetrahydrophthalic anhydride** (**3**) show similar deshielding effects of the methyl and methylene protons, respectively, in magic acid solutions. The pmr data of 2 and **3** in solutions containing varying amounts of magic acid are summarized in Table I.

It is known that acyclic and saturated cyclic acid anhydrides are cleaved in excess magic acid.[2] However, unsaturated carboxylic acid anhydrides (**1**–**3**) are not cleaved under similar conditions. Furthermore, the olefinic double bonds in **1**–**3** are not protonated in the same media. This behavior is similar to that observed in the protonation of α,β-unsaturated alde-

(7) Dimethylmaleic anhydride was made available by Dr. H. Bosshard of CIBA-GEIGY Limited, Basel, Switzerland.

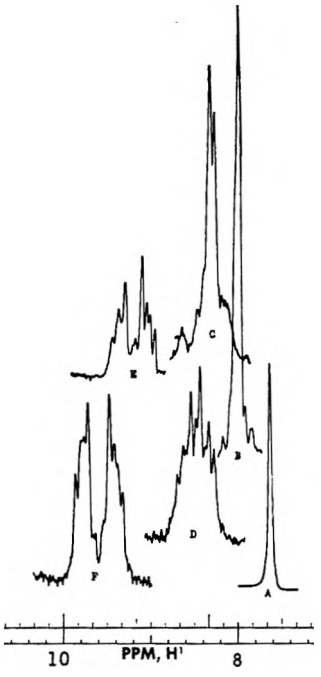
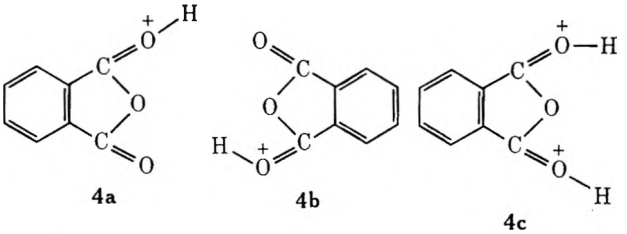


Figure 1.—Pmr spectra of phthalic anhydride (4) in SO_2 (A), in 1.0 equiv mol of magic acid (B), in 2.0 equiv mol of magic acid (C), in 4.0 equiv mol of magic acid (D), in excess magic acid (E), and in neat magic acid (F) solutions.

hydes and ketones in superacids.[8] Magic acid solutions of cyclic carboxylic acid anhydrides (**1**–**3**) when quenched with ice–water regenerate the starting anhydrides unchanged.

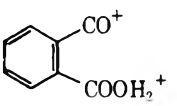
Protonation of the olefinic double bonds in unsaturated cyclic carboxylic acid anhydrides can take place only if they are not directly attached to the carbonyl groups. For example, 1,2,3,6-tetrahydrophthalic anhydride reacted with magic acid at −80° giving complicated and yet unidentified products. The pmr spectrum of the resulting solution shows the absence of olefinic protons and the presence of carboxonium groups ($COOH_2^+$).[9] These data indicate that protonation of double bond in 1,2,3,6-tetrahydrophthalic anhydride has occurred, as well as cleavage of the acid anhydride group.

Aromatic Cyclic Acid Anhydrides.—**Phthalic anhydride** (**4**) was studied with different molar equivalents of 1:1 mol/mol FSO_3H–SbF_5 in SO_2 solution at low temperature. The pmr spectra of the resulting solutions are shown in Figure 1. The deshielding of the aromatic protons (which show a singlet absorption at δ 7.73 in SO_2 solution) after protonation is proportional to the molar equivalents of magic acid used. When **4** was treated with equimolar 1:1 mol/mol FSO_3H–SbF_5 in SO_2 solution at −78°, the pmr spectrum of the solution shows a singlet absorption at δ 8.03 for the aromatic protons and a very deshielded broad singlet absorption at δ 14.0 for the rapidly exchanging OH proton. The aromatic singlet absorption was further deshielded and split into a multiplet at δ 8.35 when 2 mol equiv of 1:1 mol/mol FSO_3H–SbF_5 in SO_2 was used (Figure 1, C trace). The OH absorption is shifted upfield, presumably due to rapid exchange with the superacid system. The multiplet absorption was slightly broadened and further deshielded to δ 8.50 when 4 mol equiv of 1:1 mol/mol FSO_3H–SbF_5 in SO_2 solution was used (Figure 1, D trace). The pmr spectrum of **4** in excess 1:1 mol/mol FSO_3H–SbF_5–SO_2 became two multiplets at δ 9.38 and 9.03 (Figure 1, E trace). This solution was then added to a solution of **4** in SO_2. The pmr spectrum of the resulting solution is dependent upon the concentration of **4** in SO_2 and is similar to those previously obtained (Figure 1, B, C, and D traces). Thus, the process is reversible. Under all of the experimental conditions studied, no static OH proton absorption of either mono- or diprotonated phthalic anhydride was observed. This behavior is very similar to that of **1** in similar magic acid solutions. Thus, intermolecular hydrogen exchange processes involving mono- or diprotonated phthalic anhydride, such as **4** + **4a** ⇌ **4a** + **4**, **4a** + **4b** ⇌ **4b** + **4a**, and **4a** + H^+ ⇌ **4c** ⇌ **4b** + H^+, are taking place.



4a **4b** **4c**

Phthalic anhydride was not cleaved, however, to **4d**



4d

even in neat 1:1 mol/mol FSO_3H–SbF_5 at room temperature. The pmr spectrum of this solution shows again two further deshielded multiplets at δ 9.80 and 9.45. Quenching of the solution quantitatively regenerated starting phthalic anhydride. If **4d** would be formed or involved in the intermolecular hydrogen exchange processes, phthalic acid should have been obtained from the quenching experiment.[10]

In addition, we have also studied the behavior of phthalic acid with varying molar amounts of 1:1 mol/mol FSO_3H–SbF_5 in SO_2 solution at low temperature. The pmr spectra of either **4** or phthalic acid in the same magic acid solution are identical, except for the intense H_3O^+ peak in the latter. These data clearly show that phthalic acid dehydrated in FSO_3H–SbF_5–SO_2 solution to phthalic anhydride **4**.

Other aromatic cyclic carboxylic acid anhydrides, such as 3,6-dimethylphthalic anhydride (**5**), 1,8-naphthalic anhydride (**6**), 1,4-dimethyl-2,3-naphthalic anhydride (**7**), 1,2,4,5-benzenetetracarboxylic acid dianhydride (**8**), 1,4,5,8-naphthalenetetracarboxylic acid dianhydride (**9**), and 2,3-pyridinedicarboxylic acid anhydride (**10**), were also studied with varying molar amounts of 1:1 mol/mol of FSO_3H–SbF_5 in SO_2 solution, at low temperature. They behave very similarly to phthalic anhydride in these media. Their pmr parameters are tabulated in Table I. The aromatic, as well as the methyl, protons of **5**–**10** are increasingly more deshielded with higher molar equivalents of 1:1 mol/

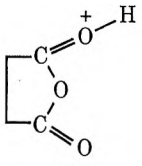
(8) G. A. Olah, Y. Halpern, Y. K. Mo, and G. Liang, *J. Amer. Chem. Soc.*, **94**, 3554 (1972).

(9) The carboxonium groups ($COOH_2^+$) generally show two nonequivalent OH absorptions at δ 12.0–13.5 [see G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 3591 (1967)].

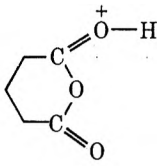
(10) A referee has pointed out, however, that quenching experiments would not exclude **4d** as a low concentration, steady-state intermediate.

mol FSO_3H–SbF_5 in SO_2 solution. Data indicate that intermolecular hydrogen exchange of monoprotonated, as well as diprotonated, aromatic cyclic carboxylic acid anhydrides with the superacid solvent system takes place. None of the cyclic carboxylic acid anhydrides **5**–**10** or tetrachloro- (bromo-) phthalic anhydride (**11**–**12**) were cleaved in the superacid solutions, even at 0°, in sharp contrast to acyclic and also saturated cyclic acid anhydrides (see subsequent discussion). Quenching of the solution again quantitatively regenerated starting anhydrides.

Saturated Cyclic Anhydrides and Their Cleavage.— Protolytic cleavage of succinic and glutaric anhydrides (**13** and **14**, respectively) has been observed in excess FSO_3H–SbF_5–SO_2 solution.[3] However, observation of protonated succinic and glutaric anhydrides **13a** and **14a**, respectively, under stable ion conditions have not

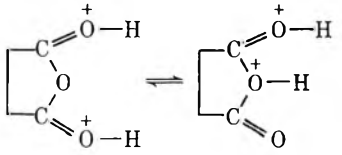


13a



14a

yet been achieved. As an extension of this work, we have now examined **13** and **14** with different molar equivalents of 1:1 mol/mol FSO_3H–SbF_5 in SO_2 solution with a hope to observe directly the mono- and diprotonated anhydrides. The pmr spectrum of **13** in SO_2 at −60° displays a singlet absorption at δ 2.73. This singlet absorption was deshielded to δ 2.90 and 3.00 when **13** was treated with 0.25 and 1.00 molar equiv amounts of 1:1 mol/mol FSO_3H–SbF_5 in SO_2 solution, respectively. Two OH absorptions were also observed at δ 14.8 and 13.2, respectively, in their pmr spectra. These data indicate that **13** was protonated and underwent intermolecular hydrogen exchange with the superacid systems. Static monoprotonated succinic anhydride **13a** was not observed even at −90°. The pmr spectra of **13** in SO_2 solutions containing 3 and 4 mol equiv of FSO_3H–SbF_5 displayed two further deshielded singlets at δ 3.80 and 4.60 (slightly broadened), respectively. These data suggest that intermolecular hydrogen exchange in these system may involve diprotonated succinic anhydride (**13b** and **13c**). Intramolecular hydrogen exchange through **13b** and **13c** is less probable. It can be suggested that diprotonated succinic anhydrides **13b** and **13c** are also involved in the cleavage reaction of **13** in large excess of superacid to give oxocarbenium–carboxonium ion $OC^+(CH_2)_2COOH_2^+$ (**13d**). The cleavage reaction of **13** in excess superacid has been reported previously.[3] Consequently, the slight broadening of the CH_2 absorption at δ 4.60 (when **13** was treated with 4 mol equiv of FSO_3H–SbF_5 in SO_2 solution) may be due to involvement of **13d**.

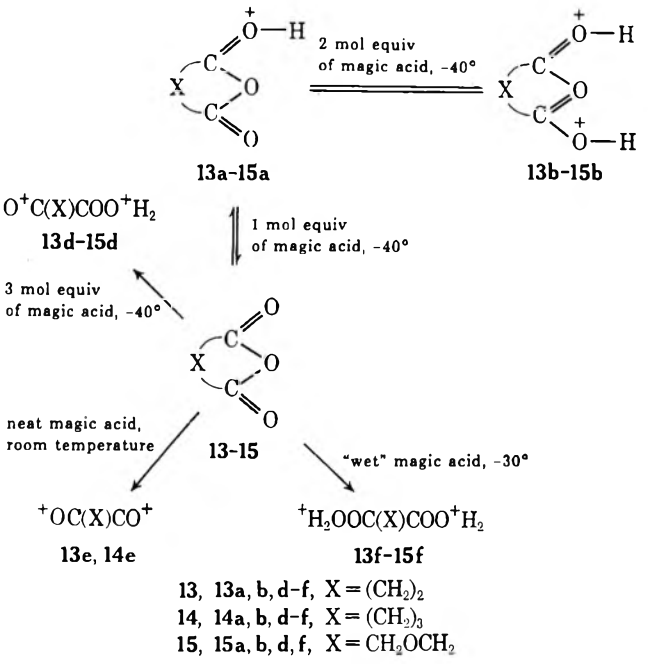


13b **13c**

When **13** was treated with "wet" magic acid (*i.e.*, containing ~10 mol % of H_3O^+), diprotonated succinic acid was formed in addition to **13d**. The amount of diprotonated succinic acid formed is proportional to the concentration of hydronium ion (H_3O^+) originally present in the magic acid solution. In neat 1:1 mol/mol FSO_3H–SbF_5 solution, at room temperature, **13** was cleaved and dehydrated to the diacyl cation, $OC^+(CH_2)_2CO^+$ (**13e**).

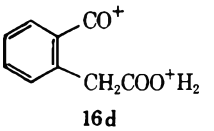
Glutaric anhydride (14) and diglycolic anhydride (15) behave very similarly to **13** with varying amounts of magic acid (Scheme I). The pmr data of **13**–**15** in

SCHEME I

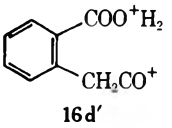


these solutions are tabulated in Table I. Diglycolic anhydride (**15**) decomposed with CO_2 evolution when treated with neat magic acid at room temperature. The ethereal oxygen atom of **15** was not observed in protonated form under any other studied conditions,[11] although it may be involved in the cleavage processes.

Protonation of homophthalic anhydride (**16**) was also studied in different magic acid media. With 1 and 2 mol equiv of 1:1 mol/mol FSO_3H–SbF_5 in SO_2 solution, **16** behaved similarly to **13**–**15**. In excess magic acid, **16** was cleaved to give equal amounts of acylcarboxonium ions **16d** and **16d′**. The pmr spectrum of the solution shows two (equal intensity) singlet absorptions at δ 4.95 and 5.05 for the methylene protons of **16d** and **16d′**, respectively. These singlet absorptions are independent of the temperature in the range from −80 to −10°, indicating that interconversion of **16d** and **16d′** through **16b** and **16c** does not occur. The OH absorptions of **16d** and **16d′** were not observed in the pmr spectra owing to rapid exchange with the acid solvent system.

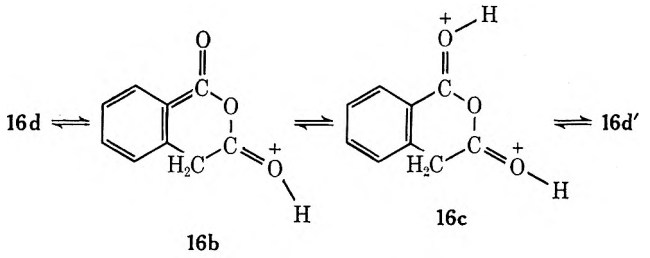


16d

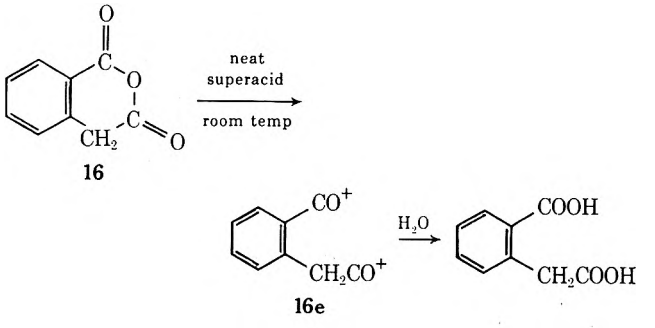


16d′

(11) G. A. Olah and D. H. O'Brien, *J. Amer. Chem. Soc.*, **89**, 1725 (1967).



In neat magic acid at room temperature, **16** was cleaved and dehydrated to the corresponding diacyl cation **16e**. The methylene protons of **16e** show a



singlet absorption at δ 5.50. Quenching of the solution with ice–water gave homophthalic acid exclusively.

In conclusion cyclic carboxylic acid anhydrides behave differently from their acyclic analogs in superacid solutions. Aromatic and unsaturated cyclic anhydrides (in which the carbonyl carbons are directly attached to the sp^2 olefinic carbons) are not cleaved, even in neat magic acid at room temperature. Maleic anhydride and related unsaturated anhydrides thus show remarkable stability in superacid media. One possible explanation is that they contain four adjacent sp^2 carbon atoms and thus favor for the formation of a five-membered ring. Even if this would be cleaved in superacid media, the recyclization process may be extremely rapid. This is evidenced by the ease of cyclodehydration of phthalic and maleic acid in neat magic acid at room temperature to the corresponding anhydrides. In contrast acyclic saturated dicarboxylic acids (such as glutaric acid) are dehydrated to diacyl cations.

Experimental Section

Materials.—Carboxylic acid anhydrides used, when not otherwise indicated, were commercial material of high purity (Aldrich Chemical Co.). They were used without further purification. Dimethylmaleic anhydride was made available by Dr. H Bosshard of CIBA-GEIGY Limited, Basel, Switzerland, and we are grateful for his assistance. 3,6-Dimethylphthalic anhydride (**4**) and 1,4-dimethyl-2,3-naphthalic anhydride (**7**) were gifts from Professor M. S. Newman. Antimony pentafluoride and fluorosulfuric acid were purified as previously described.[12] Magic acid solutions were stored in Teflon bottles.

Nmr Spectra.—A Varian Associates Model A-56/60A spectrometer with variable temperature probe was used for all spectra. Chemical shifts are reported in parts per million (δ) from external (capillary) TMS.

Protonation of Cyclic Carboxylic Acid Anhydrides.—Protonated cyclic acid anhydrides were prepared by slow addition, with efficient stirring (vortex mixer), of generally a 10% (w/w) solution of the anhydride in SO_2 to a SO_2 solution of fluorosulfuric acid–antimony pentafluoride (in proportions of the reagents indicated in Table I). Samples were transferred to a precooled nmr tube and studied by nmr.

Quenching of protonated anhydrides was carried out by adding, with efficient stirring, their solution to ice–water. The quenched products were isolated and analyzed by comparison with authentic samples of starting material or their corresponding carboxylic acids by glc, ir, and nmr. Details of all studies were similar to those reported previously in the case of acyclic anhydrides[2].

Acknowledgment.—Support of our work by the National Institutes of Health and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. Professor M. S. Newman is thanked for arousing our interest in the topic and stimulating discussion.

Registry No.—**1**, 108-31-6; **2**, 766-39-2; **3**, 2426-02-0; **4**, 85-44-9; **5**, 5463-50-3; **6**, 81-84-5; **7**, 40682-58-4; **8**, 89-32-7; **9**, 81-30-1; **10**, 699-98-9; **13**, 108-30-5; **14**, 108-55-4; **15**, 4480-83-5; **16**, 703-59-3.

(12) G. A. Olah and T. E. Kiovsky, *J. Amer. Chem. Soc.*, **89**, 5692 (1967).

Stable Carbocations. CLVIII.[1a] Degenerate 1,2-Hydrogen Shifts in Fluorobenzenium Ions and Their Comparison with Those in Methylbenzenium Ions[1b]

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Protonation of fluorinated benzenes was studied in fluoroantimonic acid SbF_5–HF (1:1 mol:mol)–SO_2ClF (1:1 v:v) solution at low temperature. Temperature dependent nmr (^1H and ^{19}F) spectra of protonated fluorobenzene, *o*- and *p*- difluorobenzene, and 1,2,3,4-tetrafluorobenzene were observed indicating stepwise 1,2-hydrogen shifts in all these benzenium ions. The activation energies for the two, different, stepwise processes in the 3,4-difluorobenzenium ion were found to be 5.7 ± 0.8 and 11.2 ± 0.9 kcal/mol.

In previous studies of protonation of fluorinated benzenes in FSO_3H–SbF_5 solution, *o*-difluorobenzene, 1,2,3,4-tetrafluorobenzene, pentafluorobenzene, and hexafluorobenzene were not observed to be protonated.[2] We have consequently applied the more suitable superacid medium, SbF_5–HF (1:1 mol:mol)–SO_2ClF (1:1 v:v), for the protonation of some weak aromatic bases.[3] The advantages of this superacid system are the increased solubility of substrate, lower freezing

(1) (a) G. A. Olah, S. Kobayashi, and Y. K. Mo, *J. Org. Chem.*, submitted. (b) A preliminary communication has appeared: G. A. Olah and Y. K. Mo, *J. Amer. Chem. Soc.*, **94**, 9241 (1972).

(2) G. A. Olah and T. E. Kiovsky, *ibid.*, **89**, 5692 (1967).

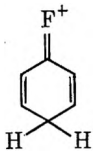
(3) G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly, and Gh. D. Mateescu, *ibid.*, **94**, 2034 (1972).

point and lesser viscosity of the medium even at very low temperatures, and the acid's protonating ability toward weak bases. The resolution of spectra of protonated fluorinated benzenes also showed marked improvement over earlier studies in neat FSO_3H–SbF_5 at low temperature and allowed observation of fine structure of spin–spin couplings. This system allowed us to carry out a systematic investigation of protonated fluorinated benzenes and the study of 1,2-hydrogen shifts in the formed ions. Temperature-dependent nmr study of fluorobenzenium ions was used to investigate the nature of intra- and intermolecular hydrogen exchange reactions.

Results and Discussion

Protonation of fluorinated benzenes was carried out in SbF–HF (1:1 mol:mol)–SO_2ClF (1:1 v:v) solution, generally at low temperatures. The nmr (^1H and ^{19}F) parameters of parent fluorobenzenes and the related fluorobenzenium ions are summarized in Tables I and II, respectively.

Fluorobenzene (1) was protonated in SbF_5–HF (1:1 mol:mol)–SO_2ClF (1:1 v:v) solution at −78° to give 4-fluorobenzenium ion 2. The nmr (^1H and ^{19}F) spectra are temperature dependent (Figure 1). The pmr spectrum of the static "frozen-out" ion 2 (at −84°) is well resolved and shows the methylene protons as a doublet at δ 5.43 (J_{HF} = 11 Hz); the coupling is due to the long-range H–F spin–spin interaction (through five bonds). The slight broadening of the CH_2 absorption indicates coupling of CH_2 to the ortho protons. The meta protons show a triplet at δ 8.33 ($J_{HH} = J_{HF}$ = 9 Hz) indicating about equal coupling to the ortho protons and the para fluorine atom. The ortho protons display a multiplet at δ 9.93. As the temperature of the solution is increased, the methylene and the ortho proton absorptions become broadened and merge into the base line at −21°. Meanwhile, the triplet of the meta protons changes to a doublet. The doublet is due to the proton–fluorine coupling. The ^{19}F nmr absorption of ion 2 shows a multiplet at ϕ 10.0 (96.3 ppm deshielded from fluorobenzene). The substantial deshielding effect is due to the resonance contribution of form 3. These results indicate that rapid 1,2-hydrogen



3

shifts occur between the CH_2 and the ortho protons. The interconversion of 2 and 2b is considered to involve two-electron, three-center bonded benzonium ion (2a) type transition states.[3,4] There is no indication, however, in the low-temperature nmr spectra for observable benzonium ion intermediates.

When the temperature of the solution of ion 2 is further raised (owing to the relatively low boiling point of SO_2ClF, 7°, these studies were carried out in neat SbF_5–HF solution), a second set of degenerate hydrogen shifts is observed. The pmr spectrum of ion 2 at −10° is essentially the same in SbF_5–HF solution

(4) G. A. Olah, *Accounts Chem. Res.*, **4**, 240 (1971).

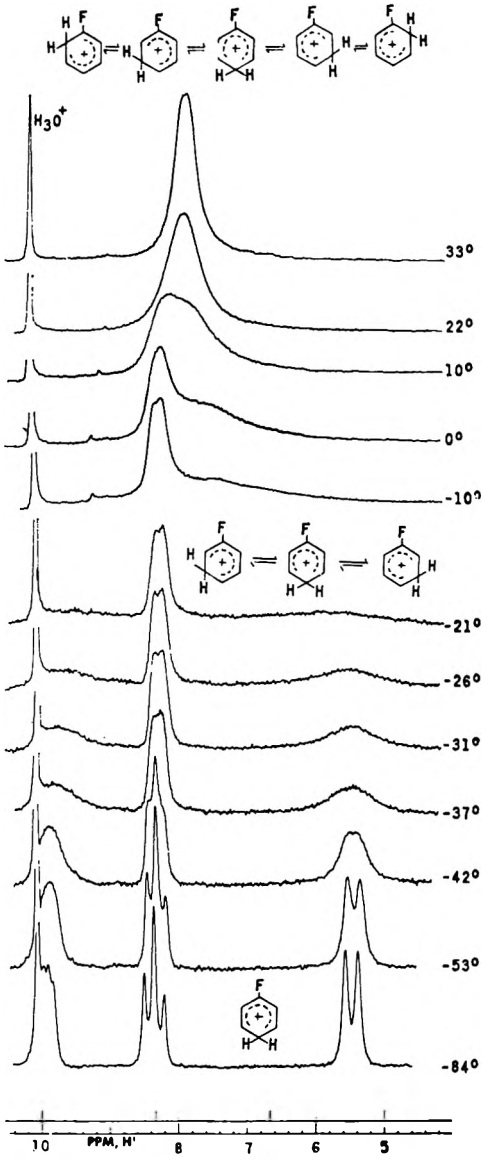
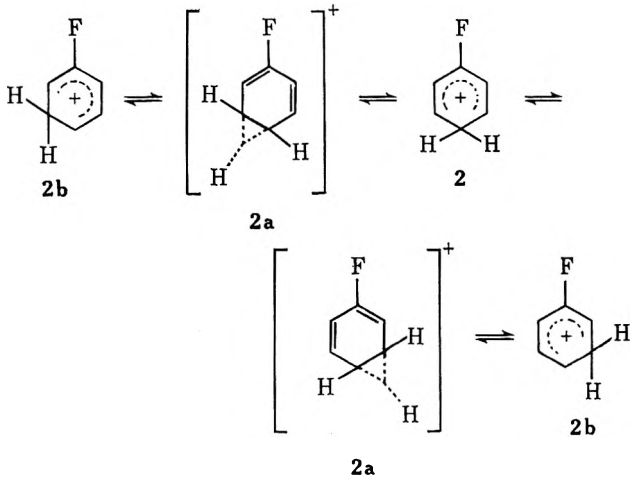


Figure 1.—Temperature-dependent pmr spectra of 4-fluorobenzenium ion 2.



2b 2a 2

2a 2b

with or without SO_2ClF as cosolvent. The meta protons will show a broadened doublet at δ 8.33. There is a very broad peak at δ 7.7 which is about equal to the average shift of CH_2 and ortho-proton absorptions [(9.93 + 5.43)/2 = δ 7.68] (due as discussed to the intramolecular 1,2-hydrogen shift between the methylene and ring hydrogens ortho to them). On further

TABLE I

PMR DATA OF FLUOROBENZENES AND THEIR FLUOROBENZENIUM IONS IN SbF_5–HF (1:1 mol:mol)–SO_2ClF (1:1 v:v) SOLUTIONS[a,b]

Registry no.	Fluorobenzene		Ion				Registry no. (ion)
			CH_2	H_{meta}	H_{ortho}	H_{para}	
462-06-6	Fluorobenzene	7.2 (m)	5.43 (d), J_{HF} = 11 Hz	8.33 (t), J_{HF} = J_{HH} = 9 Hz	9.93 (m)		18535-68-7
540-36-3	*p*-Difluorobenzene	6.78 (t)	5.73 (d), J_{HF} = 11 Hz	8.3 (br)	8.6 (br)	9.9 (br)	18535-69-8
367-11-3	*o*-Difluorobenzene	7.1 (m)	5.8 (s, br)	8.7 (br)	9.5 (br)		40719-16-2
372-18-9	*m*-Difluorobenzene	6.8 (m)	5.40 (t, d), J_{HF} = 9 Hz, J_{HH} = 2 Hz	7.90 (t), J_{HF} = 8 Hz 8.20 (t), J_{HF} = 8 Hz	9.3 (m)		18497-70-6
367-23-7	1,2,4-Trifluorobenzene	7.0 (m)	5.43 (t, br) J_{HF} = 9 Hz	7.9 (m)	8.54 (8 lines, d q) J_{HF} = 8, J_{HH} = 3 Hz		18497-72-8
372-38-3	1,3,5-Trifluorobenzene	6.7 (m)	5.30 (q), J_{HF} = 8 Hz	7.64 (8-line m)			18497-71-7
2367-82-0	1,2,3,5-Tetrafluorobenzene	6.8 (m)	5.62 (q), J_{HF} = 8 Hz	7.87 (d, t), J_{HF} = 4 and 8 Hz			18497-73-9
551-62-2	1,2,3,4-Tetrafluorobenzene	6.9 (m)	5.8 (t, br), J_{HF} = 10 Hz		8.8 (br)		40719-21-9
327-54-8	1,2,4,5-Tetrafluorobenzene	7.1 (q) J_{HF} = 8 Hz	5.8 (br)			8.7 (br)	40719-22-0
363-72-4	Pentafluorobenzene	6.9 (m)	5.8 (m)				40719-23-1

[a] Abbreviations used are: s = singlet; d = doublet; t = triplet; q = quartet; br = broad; m = multiplet. [b] Proton shifts are referred to external capillary TMS and J values are in hertz.

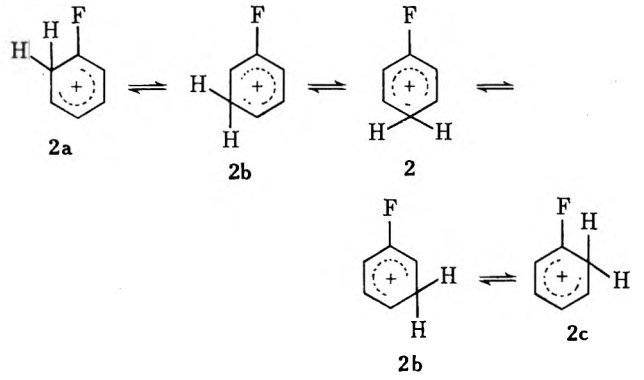
TABLE II

^{19}F NMR DATA OF FLUOROBENZENES AND THEIR FLUOROBENZENIUM IONS IN SbF_5–HF (1:1 mol:mol)–SO_2ClF (1:1 v:v) SOLUTION[a,b]

Fluorobenzene		Ion		
		H_{para}	H_{ortho}	H_{meta}
Fluorobenzene	+106.3 (m)	+10.0 (m)		
p-Difluorobenzene	+113.2 (m)	+0.5 (m)		+106.0 (m)
o-Difluorobenzene	+140.1 (m)	+32.4 (br)		+124.4 (br)
m-Difluorobenzene	+104.8	0.0 (dm), J_{FF} = 80 Hz	+7.3 (dm), J_{FF} = 80 Hz	
1,2,4-Trifluorobenzene	+108.8 (m), +152.2 (m), −133.8 (m)	+1.0 (dm), J^{m}_{FF} = 80 Hz	+18.80 (dm) J^{o}_{FF} = 80 Hz	−125.57 (dm), J^{o}_{FF} = 20 Hz
1,3,5-Trifluorobenzene	+101.0 (m)	−7.45 (t qu), J_{FF} = 70, J_{HF} = 8 Hz	+21.45 (dm), J_{FF} = 70 Hz	
1,2,3,5-Tetrafluorobenzene	+107.6 (m), +124.4 (m), +156.3 (m)	+12.4–16.6 (m)[c]	+12.4–16.6 (m)[c] +53.2 (dm), J_{FF} = 70 Hz	+152.02 (tm), J_{FF} = 20 Hz
1,2,3,4-Tetrafluorobenzene	+158.5 (dd), J_{FF} = 18.0 and 4.0 Hz +141.0 (m)	+28.0 (dd), J^{p}_{FF} − 90, J^{m}_{FF} = 24 Hz	+41.1 (dt), J^{o}_{FF} = 90, J^{m}_{FF} = 24 Hz	+143.3 (td), J^{p}_{FF} = 24, J_{HF} = 9 Hz, +137.5 (m)
1,2,4,5-Tetrafluorobenzene	+141.2 (t), J_{HF} = 8 Hz		+45.7 (br)	+121.4 (br)
Pentafluorobenzene	+164.4 (m), +156.4 (m), +140.8 (m)	+33.5 (tt), J^{o}_{FF} = 76 Hz, J^{m}_{FF} = 25 Hz	+47.6 (dm), J^{p}_{FF} = 76 Hz	+146.6 (dm), J^{p}_{FF} = 25 Hz

[a] Abbreviation used are: s = singlet; d = doublet; t = triplet; q = quartet; br = broad; m = multiplet; and qu = quintet. [b] Fluorine shifts are referred to external capillary $CFCl_3$ in parts per million and J values are in hertz. [c] See text.

raising the temperature of the solution to 10°, the broad peak at δ 7.7 collapses together with the meta-proton peak at δ 8.33 and finally (at 33°) appears as a broadened singlet at δ 7.9. This singlet absorption at δ 7.9 is also equal to the average of all the proton absorptions of ion 2 [(5.43 + 8.33 + 9.93)/3 = δ 7.9]. These data show that at this temperature, a second set of degenerate intramolecular 1,2-hydrogen shifts occurs (2c ⇌ 2b ⇌ 2a).



A comparison of the temperature-dependent nmr behavior of the 4-fluorobenzenium ion 2 and the 4-methylbenzenium ion (toluenium ion)[3] shows that both ions undergo intramolecular 1,2-hydrogen shifts. However, whereas all the ring hydrogens of the *p*-toluenium ion are rapidly exchanging with one another upon raising the temperature of the solution of the static ion to −60°,[3] this is not the case in ion 2. The 1,2-hydrogen shifts of ion 2 are taking place in a stepwise process, *i.e.*, 2 undergoes intramolecular 1,2-hydrogen shifts in two separate steps which can be separately observed by nmr spectroscopy. The difference in behavior is mainly due to the relative instability of ion 2c caused by the inductive effect of fluorine on its ortho position. In addition, this is strongly indicated by results of electrophilic aromatic substitution of fluorobenzene, generally showing high para/ortho isomer ratio.[5] Consequently, ion 2 is much more stable than ion 2c and the 4-methylbenzenium ion is only slightly more stable than the 2-methylbenzenium ion.

Difluorobenzene (4) was protonated in SbF_5–HF (1:1 mol:mol)–SO_2ClF (1:1 v:v) solution at −82° to give 2,5-difluorobenzenium ion **5**. The nmr (^1H and ^{19}F) spectra of ion **5** are also temperature dependent (Figure 2). The methylene protons of ion **5** show a doublet pmr absorption at δ 5.73 (J_{HF} = 11 Hz) owing to the ortho-fluorine coupling. It should be noted that the coupling constants of CH_2 to ortho F and para F are about equal (similar as in ion 2 and also ion **7**, see subsequent discussion). The ortho, meta, and para protons show slightly broadened absorption at δ 8.6, 8.3, and 9.9, respectively. The not completely resolved spectrum may be due to more complicated couplings (higher than first order) and viscosity of the medium. The ortho proton has a surprisingly shielded absorption (δ 8.6) when compared to that of ion 2 (δ 9.93), indicating the more important resonance contribution of **5a** over **5b**. Of course, the back donation of fluorine can also stabilize ion **5c**, as shown by the substantially deshielded (by 112.7 ppm from *p*-difluorobenzene) fluorine absorption at φ 0.5 for the ortho fluorine atom.

(5) G. A. Olah, S. J. Kuhn, and S. H. Flood, *J. Amer. Chem. Soc.*, **83**, 4581 (1961).

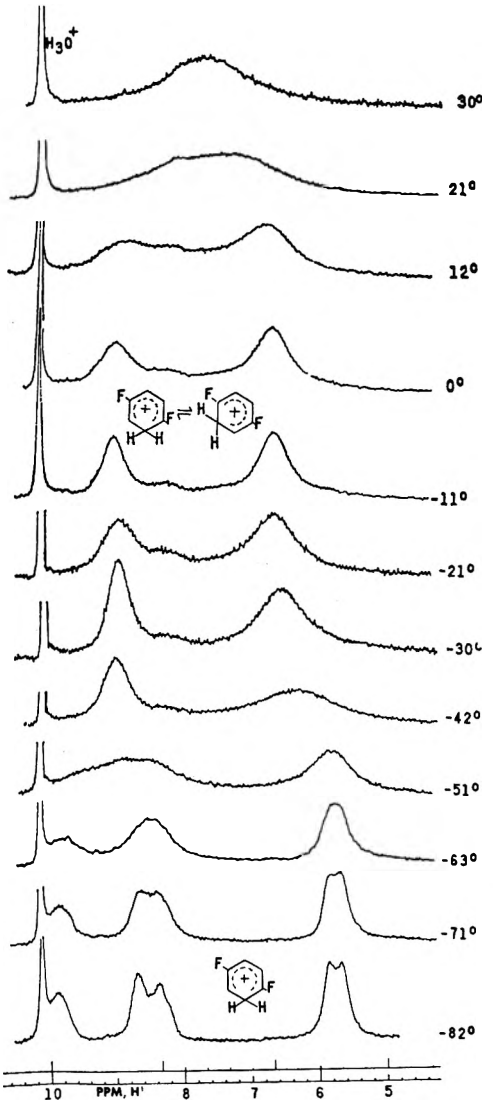
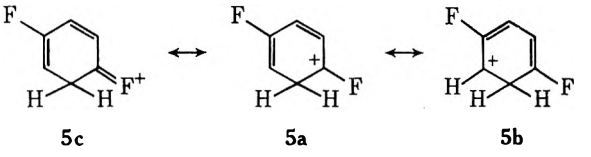
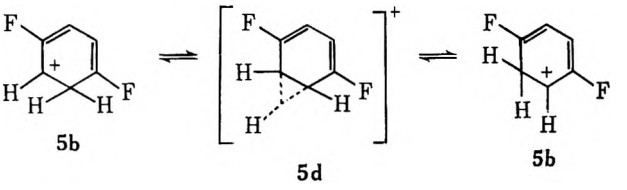


Figure 2.—Temperature-dependent pmr spectra of 2,5-difluorobenzenium ion 5.



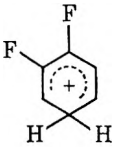
As the temperature of the solution containing ion **5** is raised, all the four proton absorptions broaden. At −11°, they appear as two slightly broadened peaks at δ 6.7 and 9.1. The ^{19}F nmr spectrum of ion **5** shows two multiplets at φ 0.5 (ortho F) and 106.0 (meta F). As the temperature of the solution is further raised, the two fluorine absorptions broaden and finally merge into the base line at −11°. The temperature-dependent behavior of ion **5** indicates that intramolecular 1,2-hydrogen shifting occurs, *via* two-electron three-center bonded benzonium ion **5d** as transition state. The exchange reaction is an intramolecular process because the observed pmr shifts at δ 6.7 and 9.1 are equal to the cal-



culated average shifts [(5.73 × 2 + 8.6)/3 = δ 6.69 and (8.3 + 9.9)/2 = δ 9.1, respectively].

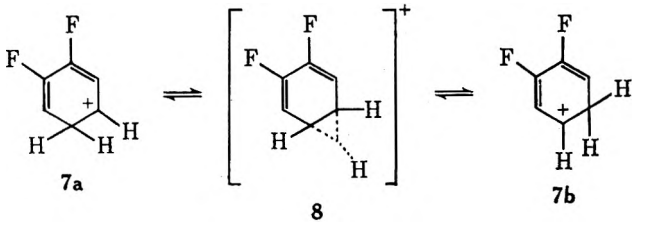
For studies at higher temperatures, we also protonated *p*-difluorobenzene (**4**) in neat SbF_5–HF solution. The pmr spectra of ion **5** are identical at −11° with or without SO_2ClF diluent. Temperature-dependent pmr spectra thus could be studied above −11° (Figure 2). The two pmr absorptions (δ 6.7 and 9.1) became broad when the temperature was raised above 0°. At 30°, they became a single very broad peak at δ 7.8 (the calculated average shift is δ 7.9). These data indicate that ion **5** also deprotonates above 0° and undergoes both intra- and intermolecular hydrogen exchange (with the solvent system).

o-**Difluorobenzene** (**6**) was protonated in HF–SbF_5 (1:1 mol:mol)–SO_2ClF (1:1 v:v) solution to give 3,4-difluorobenzenium ion **7**. The pmr spectrum of ion **7** is temperature dependent, as it is shown in Figure 3 (left). At −103°, a broadened absorption is observed at δ 5.8, corresponding to the methylene protons (as usual in benzenium ions[6-9]). In the vinylic ring proton region, two broadened absorption lines at δ 8.7 and 9.5 are observed (the resonance line at δ 10.5 being due to the oxonium ion, H_3O^+ impurity in the solvent system). The integration of peak areas gives the number of protons corresponding to each signal; the more deshielded vinylic proton absorption has twice the intensity of that of the more shielded absorption. In the ^{19}F nmr spectrum, two very broad absorptions were found at φ 32.4 and 124.4 corresponding to the fluorine shifts of para and meta fluorine atoms in fluorobenzenium ions.[2] These data clearly suggest observation of the static ("frozen-out") 3,4-difluorobenzenium ion **7**.



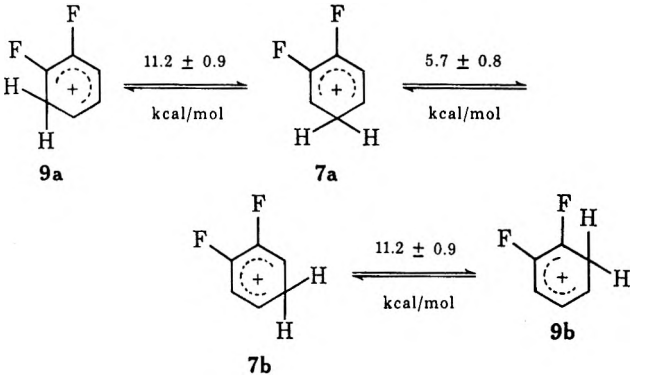
7

As the temperature of the solution was raised (*e.g.*, to −94°), the two vinylic proton absorption lines collapsed to a broadened peak at δ 9.2 and the methylene proton absorption line also broadened and became slightly deshielded. Further warming of the solution caused the methylene proton resonance to become more deshielded and also broad. Meanwhile, the deshielded vinylic proton absorption line became less broadened as the temperature was raised. At −52°, only two resolved absorption lines were observed at δ 7.1 and 9.1 with a peak area ratio of 3:2. In the ^{19}F nmr spectrum, the two absorptions became broadened as the temperature was raised and at −77° merged into the base line. These observation indicate a rapid degenerate equilibration of 3,4-difluorobenzenium ion **7** through equivalent (degenerate) forms **7a** and **7b**. The interconversion of **7a** and **7b** takes place by a 1,2-hydrogen shift *via* a transition state of benzonium ion nature (**8**).



7a **8** **7b**

As the temperature is further raised, the two absorption lines become again broad and finally collapse into a single absorption at δ 7.9 (from −52 to 0°). In the ^{19}F nmr spectrum, no new absorption lines were observed (except those of the solvent).[10] Thus, there is a second temperature-dependent dynamic process in the 3,4-difluorobenzenium ion, *i.e.*, **9a** ⇌ **7a** ⇌ **7b** ⇌ **9b**.



9a **7a** **7b** **9b**

When the exchange rate exceeds that of the nmr time scale (at 0°), then all the protons are becoming equivalent. This process also takes place through 1,2-hydrogen shifts. Since the two processes can be separately observed by pmr, the corresponding activation parameters can be obtained. The activation energies, E_a, of the two processes were calculated by a multiple-site exchange program[11] and were found to be 5.7 ± 0.8 kcal/mol with a preexponential factor, *A*, of $10^{8.9\pm0.7}$ and 11.2 ± 0.9 kcal/mol with a preexponential factor, *A*, of $10^{12.4\pm0.9}$, respectively.

In the benzenium ion[7] and alkylbenzenium ions,[3,9] both intra- and intermolecular exchanges are possible. In the case of 3,4-difluorobenzenium ion, intermolecular exchange is unlikely, even at 0°, when considering the experimental evidence of the pmr spectra. The calculated average proton shift of CH_2 and ortho H in ion **7a** or **7b** is (5.8 × 2 + 9.5)/3 = δ 7.03, in good agreement with the experimentally observed value (δ 7.1). A similar calculated average shift of one of the ortho and meta protons is δ 9.1, which is identical with the experimentally observed value. This is also the case when all protons become equivalent (at 0°). The calculated average shift is (8.7 + 9.5 × 2 + 5.8 × 2)/5 = δ 7.9. Besides the excellent agreement of pmr parameters with those calculated for intramolecular exchange processes, further evidence for the purely intra-

(6) G. A. Olah, *J. Amer. Chem. Soc.*, **87**, 1103 (1965).

(7) G. A. Olah, R. H. Schlosberg, D. P. Kelly, and G. D. Mateescu, *ibid.*, **92**, 2548 (1970).

(8) G. A. Olah and Y. K. Mo, *ibid.*, **94**, 5341 (1972).

(9) D. M. Brouwer, E. L. Mackor, and C. MacLean, in "Carbonium Ions," Vol. 2, G. A. Olah, and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1970, p 864.

(10) No ^{19}F nmr resonance was detectable for the rapidly equilibrating ions **7a** and **7b**. This is because the ortho and meta F shifts are separated by 92 ppm and the rate constant for observing the coalescence of the two signals is calculated to be 11,526 sec^{-1}. Thus, at the temperature used in this work, the rate constant is expected to be much smaller than this value. Consequently, the two resonances became too broad to be observed even at 0°.

(11) The theoretical spectra were obtained by using a Fortran IV coded program based on the equation of Gutowsky and Holm: H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956). The program was obtained originally from Dr. T. Gerig and was adapted to the Univac 1108 computer by Dr. W. E. Heyd.

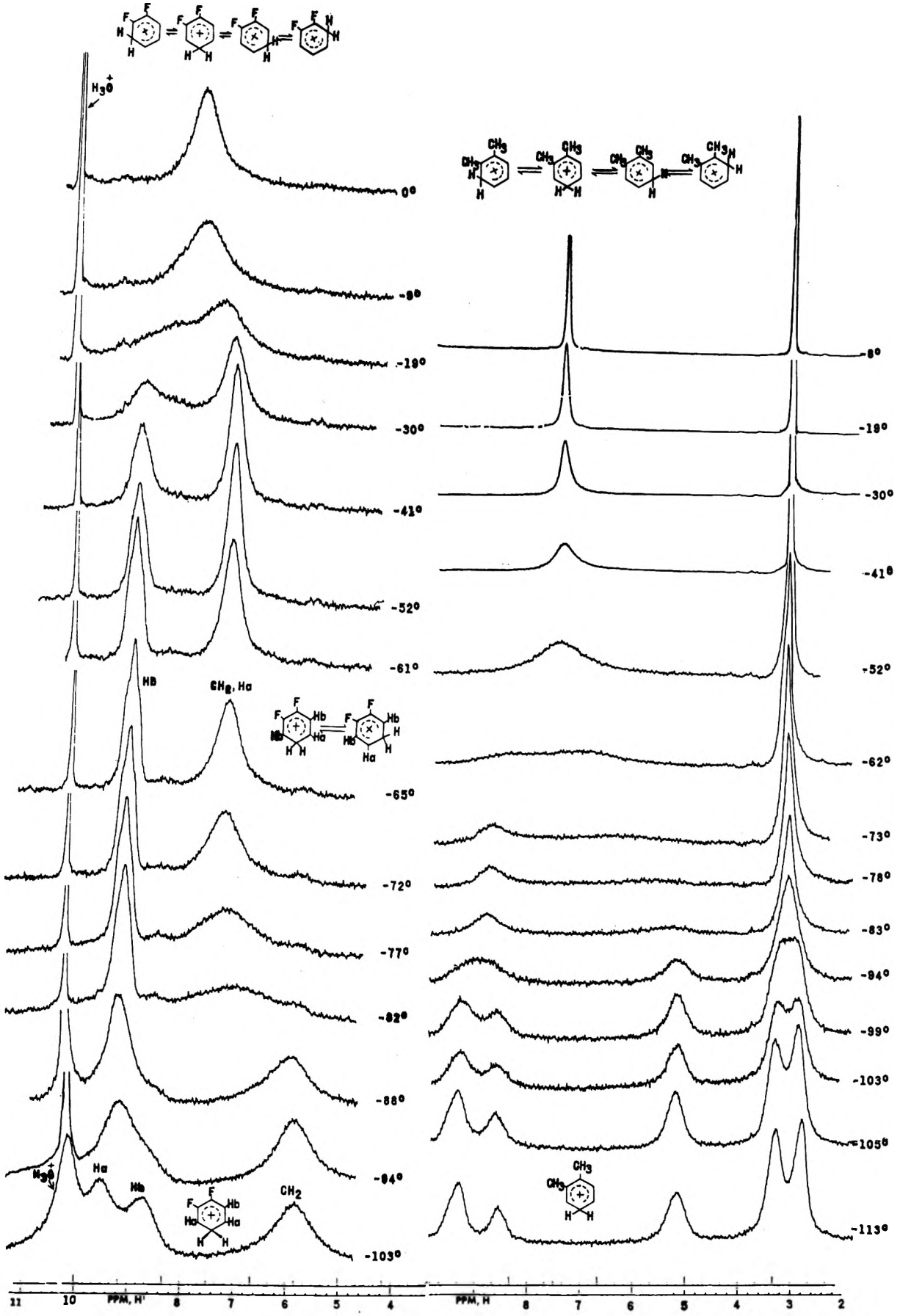


Figure 3.—Temperature-dependent pmr spectra of 3,4-difluorobenzenium ion 7 (left) and 3,4-dimethylbenzenium ion (right).

molecular nature of exchange was obtained when *o*-difluorobenzene was deuterated in DF–SbF_5–SO_2ClF solution at −78°. Deuteration was found to take place only at C-4 and C-5, as shown by the equal intensity of the two proton absorptions at δ 7.9 and 9.1 in the pmr spectrum (*vide supra*) of the d_1-3,4-difluorobenzenium ion at −61°. When the temperature of the solution was raised above −52°, the intensity of the

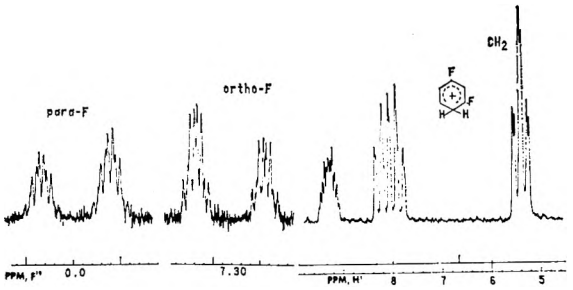
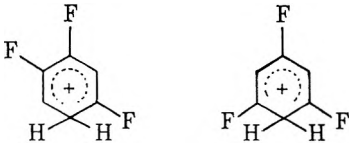


Figure 4.—^{1}H and ^{19}F nmr spectra of 2,4-difluorobenzenium ion 11.

two resonances changed. The intensity of the more deshielded absorption decreased and that of the shielded absorption increased, reaching a ratio of 2:3. At the same time, the intensity of the acid peak (present owing to a small amount of protic acid impurity in the DF–SbF_5–SO_2ClF solution) was not affected.

m-**Difluorobenzene** (**10**) was protonated in superacid at −30° to give 2,4-difluorobenzenium ion **11**. The nmr (^{1}H and ^{19}F) spectra of ion **11** are shown in Figure 4. The methylene protons of ion **11** show a triplet of doublets at δ 5.40 (J_{HF} = 9 and J_{HH} = 2 Hz), indicating that CH_2 is equally coupled to the ortho and para F but the coupling is smaller than in ions **2** and **5** (11 Hz). The small coupling (2 Hz) is due to CH_2–ortho-H coupling. The ortho proton centered at δ 9.3 shows a complicated deshielded multiplet, owing to spin–spin interactions with CH_2, meta H, and F. The two meta protons show a five-line absorption from δ 7.7 to 8.3. More careful studies show that it is actually two sets of triplets. The deshielded triplet at δ 8.2 (J_{HF} = 8 Hz) is assigned to the meta H between the two fluorine atoms, caused by their joint inductive effects. The triplet at δ 7.9 (J_{HF} = J_{HH} = 8 Hz) is then assigned to the other meta H. The ^{19}F nmr spectrum of ion **11** shows two sets of doublet of multiplets at ϕ 0.0 (para F) and 7.3 (meta F). The doublet is due to the large fluorine–fluorine coupling of 80 Hz. The nmr (^{1}H and ^{19}F) spectra of ion **11** are temperature independent from −80 to −10°.

Protonation of 1,2,4- and 1,3,5-trifluorobenzenes (**12** and **13**) in superacid at −78° gave the 2,4,5- and 2,4,6-trifluorobenzenium ions **14** and **15**, respectively. The



14 **15**

nmr (^{1}H and ^{19}F) spectra of ion **14** are shown in Figure 5. The methylene protons of ion **14** show a slightly broadened triplet at δ 5.43 (J_{HF} = 9 Hz). The proton–fluorine couplings (ortho and para) must be equal and the broadening may be due to the ortho and meta F couplings. The ortho proton of ion **14** has an eight-line multiplet at δ 8.45 and is shielded compared to that of 4-fluorobenzenium ion **2** (δ 9.93). A similar shielding effect has been observed in the 2,4-difluorobenzenium ion **5** (see previous discussion). Each of the three fluorine absorptions of ion **14** show two multiplets owing to the unusually large fluorine–fluorine coupling generally observed in fluorobenzenium ions.

The pmr spectrum of ion **15** shows a quartet at δ 5.30

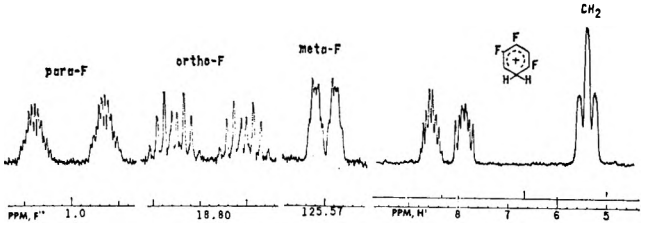
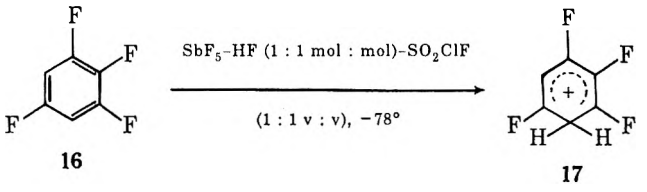


Figure 5.—^{1}H and ^{19}F nmr spectra of 2,4,5-trifluorobenzenium ion 14.

(CH_2, J_{HF} = 8 Hz) and an eight-line multiplet at δ 7.64 (meta H), indicating that methylene protons are equally coupled to the three fluorine atoms and the meta protons are coupled to all three fluorine atoms. In the ^{19}F nmr spectrum, ion **15** shows two fluorine absorptions at ϕ −7.45 (para F, triplet of quintet, J_{FF} = 70 and J_{HF} = 8 Hz) and 21.45 (ortho F, doublet of multiplet, J_{FF} = 70 Hz). The triplet of quintet of the para fluorine is due to the long-range fluorine–fluorine coupling (70 Hz) and also to the equal proton–fluorine couplings of para F–meta H and para F–CH_2. Both ions **14** and **15** show no temperature-dependent behavior from −80 to −10°.

1,2,3,5-Tetrafluorobenzene (**16**), when protonated in superacid at −78°, gave the 2,3,4,6-tetrafluorobenzenium ion **17**. The pmr spectrum of ion **17** shows



16 **17**

two well-resolved absorptions at δ 5.62 (CH_2, quartet, J_{HF} = 8 Hz) and 7.78 (meta, doublet of triplets, J_{HF} = 8 and 4 Hz). The methylene protons are equally coupled to the ortho and para fluorine atoms. The meta proton apparently couples to the adjacent fluorine atoms with equal magnitude and the small coupling could be due to the meta fluorine. The ^{19}F nmr spectrum of ion **17** shows a triplet at ϕ 152.02 (J_{FF} = 20 Hz) for the meta F which is equally coupled to the ortho and para fluorine atoms. Each peak of the triplet is a multiplet with coupling constants of less than 1 Hz, presumably owing to the spin–spin interaction of meta H and the distant ortho F. There are five multiplet fluorine absorption between ϕ 12.4 and 16.6 (with an intensity corresponding to two fluorine atoms) and these can be assigned to the para F and the ortho F, which is adjacent to the meta F. Owing to a smaller inductive effect of the other ortho F, the more shielded doublet of multiplets at ϕ 53.2 (J_{FF} = 68 Hz) was assigned to the latter. The nmr (^{1}H and ^{19}F) spectra of ion **17** are again temperature independent from −80 to −10°.

The reaction conditions for the protonation of **1,2,3,4-tetrafluorobenzene** (**18**) are important. The ratio of superacid SbF_5–HF to diluent SO_2ClF must be 1:1 (v:v) and the acid must be at least four times in excess of the substrate 1,2,3,4-tetrafluorobenzene. The pmr spectrum of protonated 1,2,3,4-tetrafluorobenzene (**19**) is temperature dependent (Figure 6A). At −83°, a slightly broadened triplet absorption is observed at δ 5.8 (2 H, J_{HF} = 10 Hz) corresponding to the methylene proton of the benzenium ion **19**. It is assumed that the

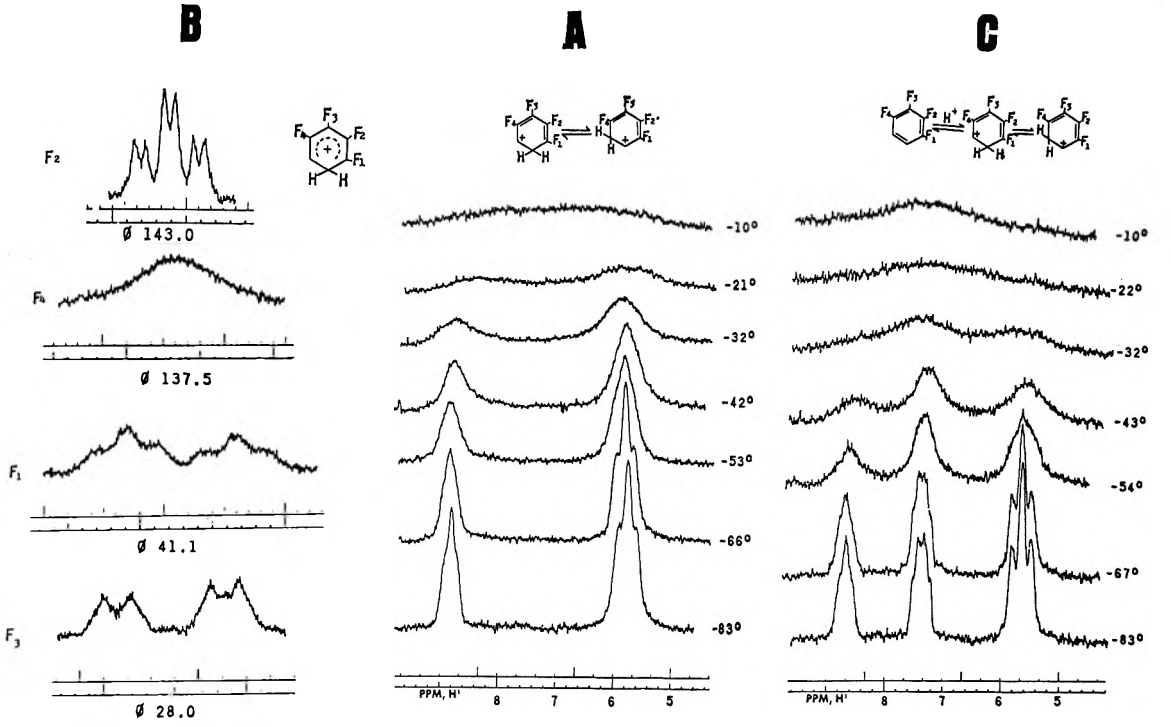
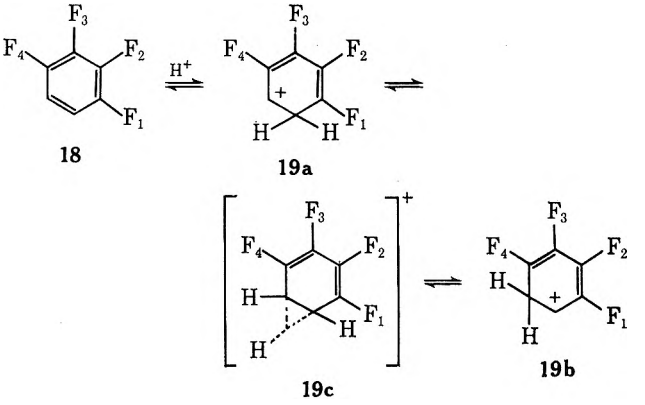


Figure 6—(A) Temperature-dependent pmr spectra of 2,3,4,5-tetrafluorobenzenium ion **19**; (B) ^{19}F nmr spectra of 2,3,4,5-tetrafluorobenzenium ion **19**; (C) temperature-dependent pmr spectra of a mixture of 1,2,3,4-tetrafluorobenzene **18** and 2,3,4,5-tetrafluorobenzenium ion **19**.

triplet is due to the CH_2 coupling with the two fluorine atoms (ortho and para). The ortho proton shows a broad absorption at δ 8.8. In the ^{19}F nmr spectrum, four fluorine absorptions were observed (Figure 6B). The most deshielded absorption at ϕ 28.0 is assigned to the para fluorine (F_3). The unusually large coupling (J_{FF} = 90 Hz) is due to the ortho,para fluorine coupling. This kind of coupling has been observed in other fluorobenzenium ions. Consequently, the ortho fluorine (F_1) is assigned to the second most deshielded fluorine absorption at ϕ 41.1. The most shielded doublet of triplet at ϕ 143.3 is assigned to the meta fluorine (F_2), since it couples to all of the fluorine atoms in ion **19** (the coupling constants of $J_{F_1-F_2}$ and $J_{F_3-F_3}$ are about equal).

As the temperature of the solution was raised (*e.g.*, −53°), the two-proton absorptions became broad and finally merged into the base line at −10°. Meanwhile, the four fluorine absorptions were also broadened and merged into the base line similarly to the pmr absorptions. In the pmr spectrum, the acid peak was also broadened and became shielded at higher temperature (−10°). The temperature-dependent nmr spectra of the solution of **18** are reversible. However, the ion is decomposed gradually at −10°. All these data indicate that both intra- and intermolecular proton exchanges of ion **19** occur. The transition state for the intramolecular hydrogen exchange again is considered to be of tetracoordinated benzonium ion nature, **19c**.

When the superacid concentration is less than 4 *M* to 1,2,3,4-tetrafluorobenzene, both parent 1,2,3,4-tetrafluorobenzene and protonated ion **19** are observed at −83°. The nmr (^1H and ^{19}F) spectra of this solution again show temperature-dependent nature (Figure 6C). Upon raising the temperature, the acid peak (not shown in Figure 6C) is also broadened and becomes shielded, indicating that an additional intermolecular



proton exchange process also takes place (**18** + **19** ⇌ **19** + **18**).

1,2,4,5-Tetrafluorobenzene (**20**) was protonated in HF–SbF_5–SO_2ClF solution at −80° to give 2,3,5,6-tetrafluorobenzenium ion **21**. The nmr spectra of ion **21** show two broadened pmr absorptions at δ 5.8 (CH_2) and 8.7 (para H) and also two broadened fluorine resonances at ϕ 45.7 (ortho F) and 121.4 (meta F). The broadening may be due to complex couplings and the viscosity of the medium at low temperature (−80°). Both proton and fluorine resonances become broader and finally merge into the base line at higher temperature (−40°). The temperature-dependent behavior can be explained in terms of **21** undergoing intermolecular hydrogen exchange with the superacid system or/and the formation of a radical cation. Since 1,2,4,5-tetrafluorobenzene (**20**) is a highly deactivated system, an intramolecular 1,2-hydrogen shift process is very unlikely. Consequently, formation of a protonation-deprotonation equilibrium can be best considered. On the other hand, when highly fluorinated aromatics (*e.g.*, tetra-, penta-, and hexafluorobenzenes) are treated with SbF_5–FSO_3H at room temperature, radical

cations are known to form.[12] This behavior is probably due to SbF_5 present in the system oxidizing the fluoroaromatic π system.

Pentafluorobenzene (22) was also protonated in $HF-SbF_5-SO_2ClF$ solution at $-78°$ to give 2,3,4,5,6-pentafluorobenzenium ion (23). The pmr spectrum of ion 23 shows a multiplet at δ 5.8, indicating the methylene protons of a benzenium ion. The pmr spectrum of 22 is also a multiplet but the aromatic proton is more deshielded (δ 6.9). In the ^{19}F nmr spectrum of ion 23, the para fluorine displays a triplet of triplets at ϕ 33.5 (J^{o}_{FF} = 76 and J^{m}_{FF} = 25 Hz) indicating that it is coupled to both ortho and meta fluorine atoms. Each peak of the triplet of triplets is slightly broadened since it also couples to the methylene protons. The ortho-fluorine absorption is less deshielded than that of para fluorine and appears as a doublet of multiplets at ϕ 47.6 (J^{p}_{FF} = 76 Hz). In addition, the meta fluorines show a doublet of multiplets ^{19}F nmr resonance at ϕ 146.6 (J^{p}_{FF} = 25 Hz). As for ion 21, both proton and fluorine absorptions of ion 23 are broadened at higher temperature, and may be due to the same explanations.

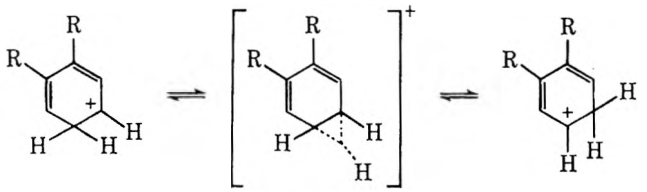
Comparison of Fluoro- and Methylbenzenium Ions.— Comparison of the nature of fluorobenzenium ions in superacids shows similarities as well as some differences to those of the corresponding methylbenzenium ions. Temperature-dependent nmr spectra of 4-fluorobenzenium ion, isomeric difluorobenzenium ions, and 2,3,4,5-tetrafluorobenzenium ion were observed in a parallel fashion with the corresponding methylbenzenium ions.

We have already discussed and compared the temperature-dependent behavior of 4-fluorobenzenium ion with 4-methylbenzenium ion. Similarly, temperature-dependent pmr spectra of 3,4-dimethylbenzenium ion were also observed, resembling closely those of 3,4-difluorobenzenium ion. Figure 3 (right) shows the temperature-dependent pmr spectra of 3,4-dimethylbenzenium ion. The degenerate 1,2-hydrogen shifts are again of intramolecular nature (within the studied temperature range). In the case of the 2,5-difluorobenzenium ion, degenerate intramolecular 1,2-hydrogen shifts were found below 0°. However, the corresponding 2,5-dimethylbenzenium ion undergoes intramolecular 1,2-hydrogen shifts only below $-74°$. On the other hand, both 2,4-dimethyl- and 2,4-difluorobenzenium ions show no intramolecular 1,2-hydrogen shift.

Temperature-dependent pmr spectra of 2,3,4,5-tetramethylbenzenium ion (prehnitenium ion) have been studied by Brouwer.[13] Degenerate intramolecular 1,2-hydrogen shifts similar to those of the 2,3,4,5-tetramethylbenzenium ion were also found in the 2,3,4,5-tetrafluorobenzenium ion.

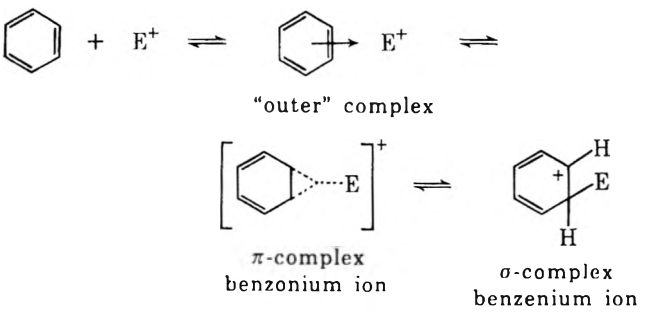
Both 2,4,6- and 2,3,5-trifluoro- and the corresponding trimethylbenzenium ions show no intramolecular 1,2-hydrogen shifts. In contrast, the 2,3,4,5,6-pentamethylbenzenium ion undergoes intramolecular 1,2-hydrogen shifts while the corresponding pentafluorobenzenium ion does not. The hexamethylbenzenium ion (protonated hexamethylbenzene) also undergoes degenerate 1,2-hydrogen shifts.[13] The analog fluorine compound, hexafluorobenzene, was not found to be protonated in any superacids studied. It formed a donor–acceptor complex with antimony pentafluoride.

In none of the studied arenium ion systems was there evidence that the "frozen-out" species at low temperature are of bridged aronium ion nature. Thus presently it seems that the 1,2-hydrogen shifts in degenerate arenium ion rearrangement proceed through a relatively high-lying bridged aronium ion state involved between the two identical arenium ion inter-



mediates. Aronium ions also play a similar role in electrophilic aromatic substitutions.

In electrophilic aromatic substitution, the electrophile (E^+) first interacts with an aromatic substrate forming a weak reagent–substrate complex ("outer" complex[14]). The formation of such complexes is reversible and does not lead to substituted products. As the reagent moves closer to bonding distance, the highest lying occupied aromatic π orbital containing an electron pair overlaps with the empty orbital of the electrophile, forming a two-electron three-center bond (π complex). The formed complex is indeed a bridged tetracoordinated carbonium ion (benzonium ion) and is identical with that involved in 1,2-hydrogen (methyl) shifts of benzenium ions. Open-



ing the three-center bond of the benzonium ion leads to the observable trivalent benzenium ion (σ complex) intermediate.

Among the three species ("outer" complex, benzonium ion, and benzenium ion) involved in electrophilic aromatic substitutions and isomerizations, "outer" complexes and benzenium ions are directly observable. Benzonium ions, however, were not yet observed under stable ion conditions.

Experimental Section

Materials—All fluorinated benzenes were commercially available (Pennisular Chemresearch) and used without further purification.

Preparation of the Ions.—Samples of the protonated fluoro-

(12) N. M. Bazhin, Yu. V. Pozdnyakovich, V. D. Shteingarts, and G. G. Yakobson, *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 10, 2300 (1969).

(13) Reference 9, p 889.

(14) Using Mulliken's definition: R. S. Mulliken, *J. Amer. Chem. Soc.*, **72**, 600 (1950); **74**, 811 (1952); *J. Phys. Chem.*, **56**, 801 (1952).

benzenes for nmr studies were prepared by adding 0.2 g of the fluorobenzene to 2 ml of SbF_5-HF-SO_2ClF solution which had been cooled at −78°. Upon warming and stirring, clear solutions were obtained.

Nmr Studies.—A Varian Associates Model A-56-60A nmr spectrometer equipped with a variable-temperature probe was used to obtain all spectra. Capillary TMS and $CFCl_3$ were used for proton and fluorine references, respectively.

Kinetic Analysis.—The activation energies for intramolecular 1,2-hydrogen shifts in protonated *o*-difluorobenzenes were determined by nmr line shape analysis. A computer stimulation of line shape was employed based on the Gutowsky-Holm[11] equation for multiple-site exchange. Activation parameters were calculated as previously described.[1b]

All the temperature-dependent nmr spectra are reversible under the studied conditions, unless otherwise mentioned.

Acknowledgment.—Support of our work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation is gratefully acknowledged.

Notes

Stable Carbocations. CLVI. Dealkylative Formation of the *tert*-Butyl Cation from Substituted *tert*-Butylbenzenes with Fluoroantimonic Acid[1]

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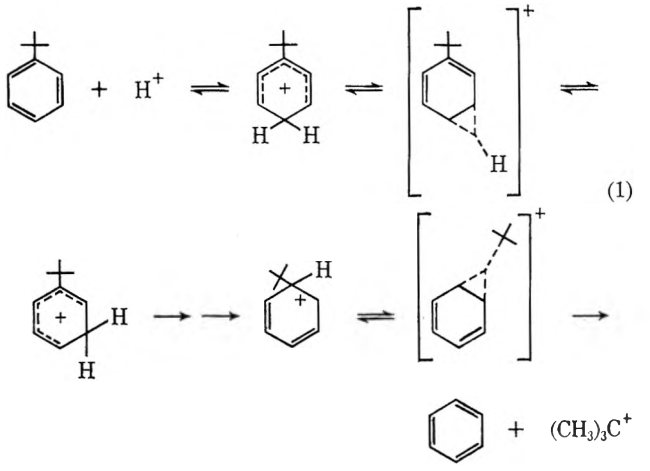
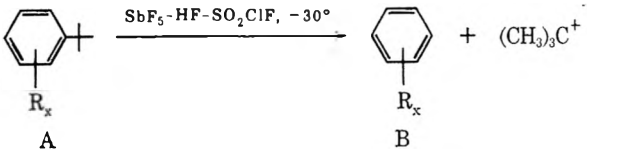
Under Friedel–Crafts reaction conditions, isomerization of di-*tert*-butylbenzene[2] and *tert*-butyltoluene[3] is well known. Under stable ion conditions, isomerization processes of alkylbenzenium ions[4] were also studied. In the study of protonation of alkylbenzenes, *tert*-butylbenzene was found to cleave readily to benzene and *tert*-butyl cation in superacid media even at low temperature.[4,5] The study of protonation of *tert*-butylbenzene in superacids at low temperature also provided direct experimental evidence for the formation of the *tert*-butylbenzenium ion. Raising the temperature results in intramolecular hydrogen migration as is shown by temperature-dependent nmr spectra. Eventually, the proton is attached to the carbon carrying the *tert*-butyl group (in all probability) and subsequently the *tert*-butyl cation is cleaved according to an α,β-cleavage mechanism (eq 1).



(1)

Ring-substituted alkylbenzenes, particularly with electron-withdrawing or sterically crowded groups, make formation of ring-protonated arenium ions increasingly difficult or even prevent it. In order to gain further insight into the protolytic behavior of *tert*-butylbenzenes with increasing substitution, we studied 17 substituted *tert*-butylbenzenes in SbF_5–HF–SO_2ClF solution at −30°. In all cases, *tert*-butyl cation was formed as evidenced by its pmr singlet absorption[2] at δ 4.0–4.2 (dependent on concentration and media). This peak was increased in intensity by adding a known solution of the *tert*-butyl cation. The pmr spectra of



A B

R_x = F_5, *o*-F, *p*-F, *p*-NH_2, *m*-$CONH_2$, *o*-, *p*-NO_2, *p*-$COCH_3$, *p*-COOH, *o*-, *m*-, *p*-*tert*-butyl, 3,5-di-*tert*-butyl, 3,5-di-*tert*-butyl-4-nitro, 3,5-di-*tert*-butyl-4-bromo, 2,4,5- and 3,4,5-tri-*tert*-butyl

the de-*tert*-butylated benzenes are identical with those of the corresponding benzenes derivatives in the same superacid media. For example, the pmr spectrum of *p*-*tert*-butylbenzoic acid in SbF_5–HF–SO_2ClF solution is identical with that of the *tert*-butyl cation and O-protonated benzoic acid in the same superacid solution.

Owing to the electron-withdrawing groups (*e.g.*, F_5, COOH, and NO_2), protonation at ring and subsequent benzenium–benzonium–benzenium ion rearrangement leading to cleavage of the *tert*-butyl group may not be necessary. Protonation may directly involve the C_{Ar}–C_α bond *via* a three-center bonded transition state (I) (thus reacting in accordance with known protolytic behavior of neopentane derivatives).

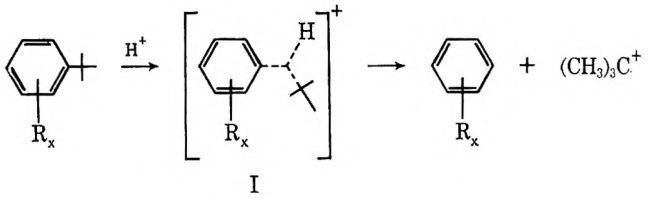
(1) Part CLV: G. A. Olah, D. A. Beal, and P. W. Westerman, *J. Amer. Chem. Soc.*, **95**, 3387 (1973).

(2) G. A. Olah, C. G. Carlson, and J. C. Lapierre, *J. Org. Chem.*, **29**, 2687 (1964).

(3) G. A. Olah, N. W. Meyer, and N. A. Overchuk, *J. Org. Chem.*, **29**, 2310 (1964).

(4) For a review and references see D. M. Brouwer, E. L. Mackor, and C. MacLean in "Carbonium Ions," G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1970, p 865.

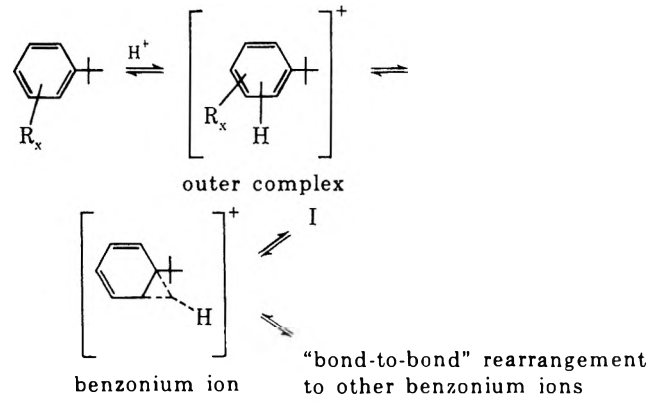
(5) G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly, and G. D. Mateescu, *J. Amer. Chem. Soc.*, **94**, 2034 (1972), and references cited therein.



I

R_x are deactivating groups

Alternatively, initial interaction of the protonating agent with the deactivated or sterically crowded ring could form an outer complex[6] in equilibrium with an oriented π complex (benzonium ion[7]), then undergo intramolecular "bond-to-bond" rearrangement[8] and lead to the formation of I.



outer complex

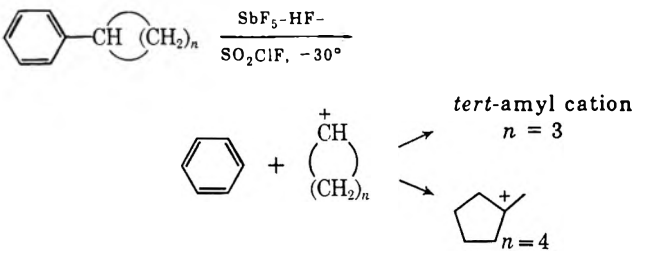
benzonium ion

"bond-to-bond" rearrangement to other benzonium ions

Our proposed mechanism is based on the fact that the formation of σ complexes (benzenium ions) in these systems is difficult or even does not take place. For example, we recently studied the protonation of pentafluorotoluene in superacid media and found no ring protonation.[9] Indeed, pentafluorotoluene underwent protolytic cleavage in superacids to give pentafluorobenzyl cation, $C_6F_5CH_2^+$, and H_2. Thus, the protolytic cleavage of pentafluoro-*tert*-butylbenzene in superacid to give *tert*-butyl cation and pentafluorobenzene may not involve any ring protonation. In other cases [$XC_6H_4C(CH_3)_3$, X = NO_2, COOH, $COCH_3$, NH_2, etc.], protonation may proceed at the n-donor side chain sites in preference to the π-donor ring. The corresponding benzenium ions (σ complexes) of these deactivated benzenes were never directly observed. Consequently, we conclude that dealkylation of these deactivated *tert*-butylbenzenes may also not involve any ring protonation prior to C_{Ar}–C_α bond protolysis.

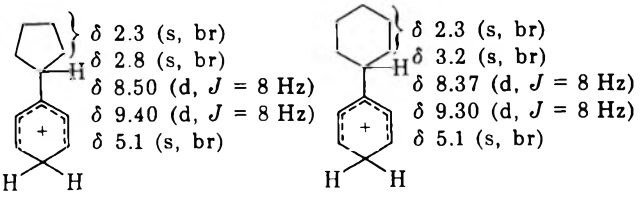
Poly-*tert*-butylbenzenes such as 1,2,4,5- and 1,3,4,5-tetra-*tert*-butylbenzenes also cleaved to benzene and the *tert*-butyl cation in fluoroantimonic acid. As initial benzenium ion formation in these sterically crowded systems is unfavorable, protolytic cleavage may involve similar σ-bond reactivity as in the case of deactivated *tert*-butylbenzenes.

Cyclopentyl- and cyclohexylbenzenes behave very much as tertiary alkylbenzenes when treated with SbF_5–HF–SO_2ClF solution at −30°. Protolytic C_{Ar}–C_α bond cleavage takes place forming, besides benzene, *tert*-amyl and methylcyclopentyl cations, respectively. Under these conditions, the initially formed cyclohexyl and cyclopentyl cations are known to rearrange to give methylcyclopentyl and *tert*-amyl cations, respectively.[10] The driving force for C_{Ar}–C_α over C_α–H protolysis (the corresponding 1-methyl-1-cycloalkyl cation is a known very stable ion) must be the higher reactivity of the C–C bond. The initial protonation in cycloalkylbenzenes is on the aromatic ring, as they can be protonated in superacid at −78° to give the stable cycloalkylbenzenium ions. The pmr spectra of the ions are in accordance with their structures.



tert-amyl cation $n = 3$

$n = 4$



In conclusion, our study on dealkylation of substituted *tert*-butylbenzenes under stable ion conditions proves that *tert*-alkylcarbenium ions are indeed involved in Friedel–Crafts isomerization of alkylbenzenes.

Experimental Section

Materials.—All the substituted *tert*-butylbenzenes were either commercially available materials (Aldrich Chemical Co.) or prepared according to the literature. Cyclopentyl- and cyclohexylbenzenes were obtained from Aldrich Chemical Co. Antimony pentafluoride (Allied Chemical Co.) was triply distilled before used. HF was obtained from J. T. Baker Chemical Co. The preparation of anhydrous fluoroantimonic acid has been described previously.[11] Spectrograde $HSbF_6$ was obtained from Cationics Inc.

Dealkylation of Substituted *tert*-Butylbenzenes with Fluoroantimonic Acid.—HF–SbF_5 (1.5 ml) was diluted with an equal volume of sulfuryl chloride fluoride (SO_2ClF) at −78°. To the resulting cold solution was added with vigorous stirring the substituted *tert*-butylbenzene (*ca.* 0.2 ml, 0.2 g) at −30°. The clear solution which formed was transferred to an nmr tube for spectral studies.

Ions not described in detail (pmr spectra) in this paper were already reported and characterized in our previous studies.

Nmr spectra were obtained on a Varian A-56-60A nmr spectrometer equipped with a variable-temperature probe. Chemical shifts are referred to external capillary TMS.

Acknowledgment.—The support of our work by the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Registry No.—A (R_x = F_5), 40782-24-9; A (R_x = *o*-F), 320-11-6; A (R_x = *p*-F), 701-30-4; A (R_x = *p*-NH_2), 769-92-6; A (R_x = *m*-$CONH_2$), 40782-26-1; A (R_x = *o*-NO_2), 1886-57-3; A (R_x = *p*-NO_2), 3282-56-2; A (R_x = *p*-$COCH_3$), 943-27-1; A (R_x = *p*-COOH), 98-73-7; A (R_x = *o*-*tert*-butyl), 1012-76-6; A (R_x = *m*-*tert*-butyl), 1014-60-4; A (R_x = *p*-*tert*-butyl), 1012-72-2; A (R_x = 3,5-di-*tert*-butyl), 1460-02-2; A (R_x = 3,5-di-

(6) Using Mulliken's definition: R. S. Mulliken, *J. Amer. Chem. Soc.*, **72**, 600 (1950); *J. Phys. Chem.*, **56**, 801 (1952).

(7) G. A. Olah, *Accounts Chem. Res.*, **4**, 240 (1971).

(8) G. A. Olah, *J. Amer. Chem. Soc.*, **94**, 808 (1972).

(9) G. A. Olah and Y. K. Mo, *J. Amer. Chem. Soc.*, in press.

(10) (a) G. A. Olah, J. M. Bollinger, C. A. Cupas, and J. Lukas, *J. Amer. Chem. Soc.*, **89**, 2692 (1967); (b) G. A. Olah and J. Lukas, *ibid.*, **90**, 933 (1968).

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

tert-butyl-4-nitro), 4074-25-3; A (R_x = 3,5-di-*tert*-butyl-4-bromo), 3975-77-7; A (R_x = 2,4,5-tri-*tert*-butyl), 796-97-4; A (R_x = 3,4,5-tri-*tert*-butyl), 40782-30-7; B (R_x = F_5), 363-72-4; B (R_x = F), 462-06-6; B (R_x = NH_2), 62-53-3; B (R_x = $CONH_2$), 55-21-0; B (R_x = NO_2), 98-95-3; B (R_x = $COCH_3$), 98-86-2; B (R_x = COOH), 65-85-0; B (R_x = *tert*-butyl), 98-06-6; B (R_x = *m*-di-*tert*-butyl), 1014-60-4; B (R_x = 1,3-di-*tert*-butyl-2-nitro), 15141-43-2; B (R_x = 1,3-di-*tert*-butyl-2-bromo), 19715-32-3; B (R_x = 1,2,4-tri-*tert*-butyl), 1459-11-6; B (R_x = 1,2,3-tri-*tert*-butyl), 40782-34-1; *tert*-butyl cation, 14804-25-2.

Cleavage of Allyloxycarbonyl Protecting Group from Oxygen and Nitrogen under Mild Conditions by Nickel Carbonyl

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Received May 15, 1973

This note outlines a method for the use of the allyloxycarbonyl group for protection of hydroxyl and amino functions.

Allyl and cinnamyl acetates have been reported to react with nickel carbonyl at 45–65° in tetrahydrofuran for 2–3 hr to form the allylic coupling products (1,5-hexadienes) in 30–50% yield.[1] Under these conditions nonallylic acetates and allylic alcohols or ethers are unreactive. These facts suggest that the allyloxycarbonyl group could be used for hydroxyl or amino protection in a way parallel to the well-known benzyloxycarbonyl (carbobenzoxy) group and removed under mild aprotic conditions by the action of nickel carbonyl or a related "allylophilic" reagent. Experimental verification of this possibility was readily obtained. The conversion of a variety of alcohols to alkyl (or cycloalkyl) allyl carbonates could be accomplished in high yield by reaction with allyl chloroformate (available from Polysciences, Inc., Warrington, Pa.) and pyridine in a suitable aprotic solvent [*e.g.*, ether or tetrahydrofuran (THF)]. Regeneration of alcohol from the corresponding alkyl allyl carbonate occurred upon exposure to nickel carbonyl, as expected, but it was found that the reaction could not be driven to completion even with an excess of the reagent. This difficulty could be overcome by the addition of *N,N'*-tetramethylethylenediamine to reaction mixtures in either acetonitrile or dimethylformamide (DMF) as solvent, although an excess of nickel carbonyl was found still to be necessary.[2] For optimal yields of alcohols from alkyl allyl carbonates, the following reaction conditions were typically employed: (a) *ca.* 5 equiv of nickel carbonyl and 3 equiv of tetramethylethylenediamine per equiv of allyl carbonate, (b) DMF [5–10 ml/ml of $Ni(CO)_4$] as solvent at 55°, (c) nitrogen or argon atmosphere, (d) *ca.* 4 hr reaction time. Under these quite mild conditions the following cleavages of alkyl allyl carbonates to alcohols were observed (yield in parentheses).

$$ROCOOCH_2CH{=}CH_2 \xrightarrow{Ni(CO)_4} ROH$$

R = *n*-decyl (95%)
R = *exo*-2-norbornyl (87%)
R = menthyl (91.5%)

To illustrate the use of the allyloxycarbonyl group for protection of amino nitrogen, two substrates, *N*-allyloxycarbonyl-*dl*-phenylalanine[3] and *N*-allyloxydicyclohexylamine, were prepared and treated with nickel carbonyl under the conditions outlined above except for the use of DMF–water (95:5) as medium and 10 equiv of nickel carbonyl. The expected free amino compounds, *dl*-phenylalanine and *N,N*-dicyclohexylamine, were obtained in 95 and 83% yield.

We expect that for large-scale preparative work where the use of excess nickel carbonyl may be unacceptable, the use of a carbon monoxide atmosphere under pressure is advisable to stabilize the reagent.

Experimental Section

The following procedures for the synthesis and cleavage of the allyloxycarbonyl derivative of 1-decanol could also be applied to *exo*-2-norborneol and menthol.

Decyl Allyl Carbonate.—A magnetically stirred solution of 1-decanol (3.24 g, 20.5 mmol) and pyridine (2.03 g, 25.7 mmol) in 75 ml of THF was cooled to 0°, and allyl chloroformate (3.097 g, 25.7 mmol) in 10 ml of THF was added dropwise. The reaction mixture was slowly warmed to room temperature, and after 2 hr at room temperature the solution was filtered and solvent was removed at reduced pressure. Ether (25 ml) was then added and the solution was filtered again, washed with water and brine, dried over anhydrous $MgSO_4$, then distilled to give 4.54 g (91%) of a pleasant-smelling liquid: bp 109–110° (0.5 mm); ir (neat) 1751 (s), 1647 (w), 1292 (sh), 1250 (s, b), 970 (m), 795 cm^{-1} (m); nmr (CCl_4) δ 6.34–5.70 (9-line multiplet, 1 H), 5.37 (ABC triplet, 2 H), 4.61 (d, J = 5 Hz, 2 H) (these three absorbances are due to the allyl group and are the same in all the carboallyloxy derivatives made), 4.14 (t, J = 6 Hz, 2 H), 1.33 (s, 16 H), 0.97 (m, 3 H); mass spectrum m/e 140 [$(CH_2)_{10}^+$].

1-Decanol.—(Nickel carbonyl is both volatile and toxic; all operations involving it were performed in a well-ventilated hood.) Into a 25-ml flask fitted with a side arm and reflux condenser topped by a three-way stopcock opened to an argon-filled balloon were placed *n*-decyl allyl carbonate (0.288 g, 1.19 mmol), tetramethylethylenediamine (0.417 g, 3.60 mmol), and 7 ml of dry, argon-saturated DMF. Nickel carbonyl (0.78 ml, 6.0 mmol) was added all at once, and the stirred mixture was warmed slowly to 55°. After 4 hr excess nickel carbonyl was removed by codistillation with ether into an ethereal iodine solution. The mixture was poured into 20 ml of water and extracted twice with 15 ml of pentane. The pentane layer was washed with 20 ml of 1 *N* hydrochloric acid and brine, and dried over anhydrous $MgSO_4$. Evaporation of the solvent at reduced pressure gave 0.177 g (95%) of 1-decanol, homogeneous by tlc and with spectral properties identical with those of authentic material.

Cleavage of Allyloxycarbonyl Amides. A. *N*-Allyloxycarbonyl-*N,N*-dicyclohexylamine.—The above procedure was followed except that 0.3 ml of water was also added to the reaction mixture, and 10 equiv of nickel carbonyl was used. After removal of excess nickel carbonyl, the reaction mixture was poured into 20 ml of 1 *N* HCl, and the solution was made basic with sodium carbonate and extracted thrice with pentane. These pentane extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give dicyclohexylamine (95% yield).

B. *N*-Allyloxycarbonyl-*dl*-phenylalanine.—The reaction conditions were as described just above. After 5 hr excess nickel carbonyl and TMEDA were removed under reduced pressure. Then 50 ml of water was added and H_2S was bubbled through the solution for 10 min. The solution was brought to pH 6, heated

(1) N. L. Bauld, *Tetrahedron Lett.*, 859 (1962).

(2) The role of tetramethylethylenediamine in this regard is unclear. It was originally considered that the formation of Ni(II) as a reaction product might somehow inhibit the reaction and that the diamine might prevent such inhibition by complexation. However, it has been observed that added nickel acetate has no effect on the rate or extent of reaction between alkyl allyl carbonate and nickel carbonyl alone.

(3) C. M. Stevens and R. Watanabe, *J. Amer. Chem. Soc.*, **72**, 725 (1950).

to break the nickel sulfide colloid, and filtered through Celite. The filtrate was evaporated under reduced pressure, and the residual solid was washed three times with acetone and dried to give pure *dl*-phenylalanine (83% yield) identified by comparison with an authentic sample.

Acknowledgment.—This work was assisted financially by the National Science Foundation.

Registry No.—$Ni(CO)_4$, 13463-39-3; decyl allyl carbonate, 40940-42-9; 1-decanol, 112-30-1; allyl chloroformate, 2937-50-0; *N*-allyloxycarbonyl-*N*,*N*-dicyclohexylamine, 40940-43-0; *N*-allyloxycarbonyl-*dl*-phenylalanine, 40940-57-6.

Selective Cleavage of Allyl Ethers under Mild Conditions by Transition Metal Reagents

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Received May 15, 1973

The highly selective properties of various transition metal derived reagents would seem to recommend their application to the removal of suitable chosen protecting groups.[1] This note outlines a new method for the selective cleavage of allyl ethers to alcohols under conditions sufficiently mild so that alcohol derivatives such as alkyl ethers, aryl ethers, or esters, and also many of the common functional groups, would not be affected. Our findings suggest that protection of hydroxyl groups as allyl ethers may be a very useful technique for organic synthesis.

We have found that rhodium(I) complexes such as $RhCl(PPh_3)_3$ catalyze the isomerization of allyl ethers (**1**) to 1-propenyl ethers (**2**) under neutral aprotic conditions.[2] Hydrolysis of the enol ethers **2** occurs rapidly at pH 2 to form the free alcohols **3**. The generality of the process was demonstrated for the allyl ethers of methanol, 1-decanol, and cholesterol, all of which could be converted readily to the corresponding alcohols **3** in >90% yield. Benzyl ethers were found to be stable under the conditions which cleave allyl ethers. Tristriphenylphosphine rhodium chloride was considerably more active as a catalyst than $RhCl_3$,[3] which in turn was more active than $PdCl_2$, $RuCl_3$, or $IrCl_3$. Prior to this work the cleavage of allyl ethers has been effected by the conventional method using strong acids, by oxidation with SeO_2 in acetic acid–dioxane,[4] or by treatment with strong base to generate an enol ether followed by acid hydrolysis or oxidation.[2,5]

$$\underset{\mathbf{1}}{ROCH_2CH{=}CH_2} \xrightarrow{Rh(I)} \underset{\mathbf{2}}{ROCH{=}CHCH_3} \xrightarrow{pH\ 2} \underset{\mathbf{3}}{ROH} + CH_3CH_2CHO$$

Experimental Section

Cleavage of Allyl Ethers as Illustrated by Menthyl Allyl Ether → Menthol.—A solution of menthyl allyl ether (0.114 g, 0.58 mmol) (prepared from menthol, sodium hydride, and allyl bromide), $RhCl(PPh_3)_3$ (0.037 g, 0.040 mmol) (Alfa Inorganics), and diazabicyclo[2.2.2]octane (0.013 g, 0.120 mmol)[6] in 10% aqueous ethanol was heated at reflux for 3 hr. An aliquot was injected into 1 *N* HCl and after a few minutes was assayed by vpc analysis (10 ft × 0.125 in. 5% Carbowax 20M Chromosorb W, 130°) which showed only menthol and menthyl allyl ether in 93 and 7% yield, respectively. Work-up of a parallel reaction (by pouring into water, extracting with ether, washing the ether with brine acidified to pH 2, drying over anhydrous $MgSO_4$, concentration, and separation on silica gel) gave menthol in 93% yield. The same procedure was applied to the cleavage of the allyl ethers of 1-decanol and cholesterol to form the alcohols in 96 and 90% yield, respectively.

Acknowledgment.—This work was assisted financially by the National Science Foundation.

Registry No.—$RhCl(PPh_3)_3$, 14694-95-2; menthyl allyl ether, 40940-58-7; allyl decyl ether, 3295-96-3; allyl cholesteryl ether, 25092-65-3.

(1) For an earlier application involving a metal-ion sensitive protecting group, see E. J. Corey and R. L. Dawson, *J. Amer. Chem. Soc.*, **84**, 4899 (1962).

(2) Allyl ethers have been found previously to be isomerized to 1-propenyl ethers under quite drastic conditions (potassium *tert*-butoxide in dimethyl sulfoxide at 100°). See J. Cunningham, R. Gigg, and C. D. Warren, *Tetrahedron Lett.*, 1191 (1964), and references cited therein.

(3) A. J. Birch and G. S. R. Rao, *Tetrahedron Lett.*, 3797 (1968); J. F. Biellmann and M. J. Jung, *J. Amer. Chem. Soc.*, **90**, 1673 (1968).

(4) K. Kariyone and H. Yazawa, *Tetrahedron Lett.*, 2885 (1970).

(5) R. Gigg and C. D. Warren, *J. Chem. Soc. C*, 1903 (1968).

(6) Added to inhibit premature hydrolysis of the intermediate enol ether. Free propionaldehyde reacts with $RhCl(PPh_3)_3$ to form the catalytically much less active $RhCl(PPh_3)_2CO$.

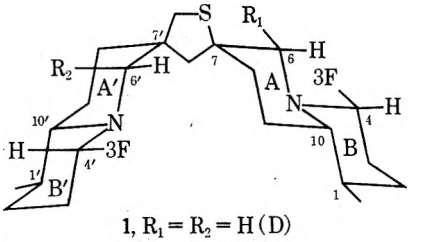
See Editorial, *J. Org. Chem.*, **38**, No. 19, 4A (1972)

Absolute Configuration of C_{30}, Sulfur-Containing Nuphar Alkaloids Determined by Circular Dichroism[1]

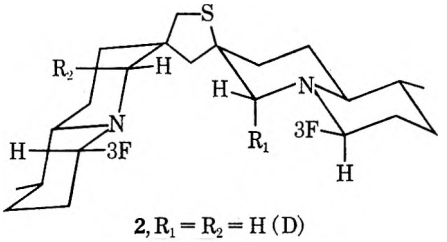
Summary: The circular dichroism resulting from an α-thioimmonium ion function was studied in 6-hydroxythiobinupharidine, 6,6′-dihydroxythiobinupharidine, and 6,6′-dihydroxythionuphlutine B to determine the absolute stereochemistry of thiobinupharidine and thionuphlutine B.

Sir: We have recently reported in detail the evidence for the relative stereochemistry of the C_{30}, sulfur-containing alkaloids thiobinupharidine (**1**) and thionuphlutine B (**2**).[2] An appreciation of the influence of sulfur–immonium ion interaction was instrumental in arriving at these structures. Manifestations of the interaction were (1) the demonstrated stereospecificity of the deuteride reduction of the bishemiaminals **3** and **4** to **1** and **2**, respectively, and (2) the appearance of the acid-induced bands in the 290–300-nm region of the uv of **3** and **4** as well as the naturally occurring monohemiaminal **5** and the model compounds **6** and **7**.

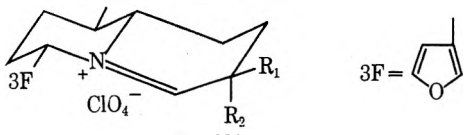
Measurement[3] in 95% ethanol of the CD of the immonium perchlorates derived from the hemiaminals mentioned above provides data which allow the assignment of the absolute configuration to these C_{30} alkaloids.



1, $R_1 = R_2 = H$ (D)
3, $R_1 = R_2 = OH$
5, $R_1 = OH$; $R_2 = H$



2, $R_1 = R_2 = H$ (D)
4, $R_1 = R_2 = OH$



6, $R_1 = SCH_3$; $R_2 = CH_3$
7, $R_1 = CH_3$; $R_2 = SCH_3$
8, $R_1 = OH$; $R_2 = CH_3$

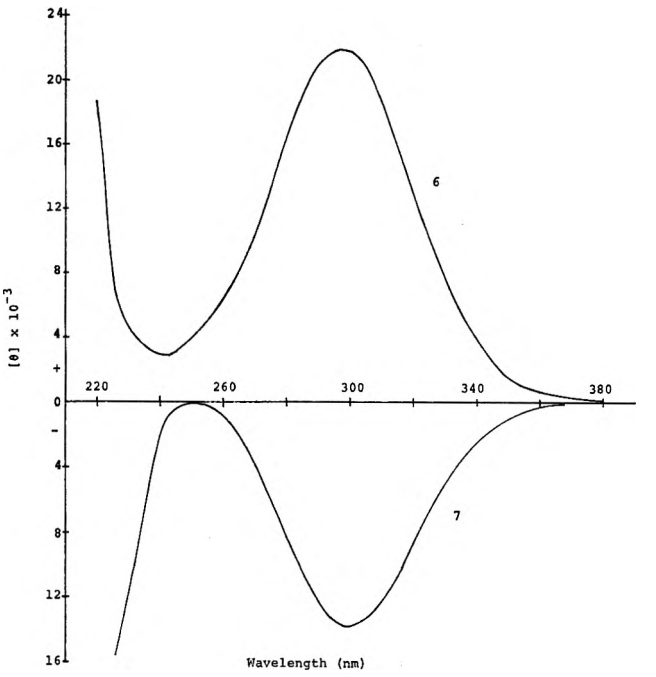


Figure 1.—The circular dichroism of immonium perchlorates derived from 7β-methylthiodeoxynupharidin-6α-ol (**6**) and 7α-methylthiodeoxynupharidin-6β-ol (**7**).

Thus the pseudoenantiomeric pair of perchlorates **6** and **7** give, respectively, positive ($[\theta]_{298}^{25}$ 22,000, *c* 1.5 mg/10 ml) and negative ($[\theta]_{300}^{25}$ −14,000, *c* 0.8 mg/5 ml) CD bands as shown in Figure 1. The relative configuration of the C_7 sulfur atom in **6** and in the immonium ions derived from **3** and **5** is the same. On the other hand, the relative configuration of the sulfur atom in **7** and in the immonium ion from **4** is the same but different from that of **3**, **5**, and **6**.[2] Since **6** and **7** are derived from (−)-deoxynupharidine whose absolute configuration has been established[4,5] (1*R*,4*S*,7*S*,10*S*), the set of curves given in Figure 1 can be used as comparison standards for ascertaining the absolute stereochemistry of other α-thioimmonium ions of the nuphar alkaloid series. Significantly the immonium ion **8** also gives a positive CD band ($[\theta]_{230}^{25}$ 8800) but at a much lower wavelength, a result consistent with the report that simple immonium ions absorb in the uv in the 220–230-nm region[6] and our earlier observation that interaction of sulfur with an immonium ion is necessary for the appearance of the longer wavelength absorption in the 300-nm region.[2]

As the curves of Figure 2 show, perchlorates derived from bishemiaminal **3** and monohemiaminal **5** give

(1) Support of this work by the National Institutes of Health, U. S. Public Health Service (Grant No. AI10188) is gratefully acknowledged.

(2) R. T. LaLonde, C. F. Wong, and K. C. Das, *J. Amer. Chem. Soc.*, in press.

(3) CD measurements were performed on a Jasco Model 5 spectropolarimeter at the concentrations indicated.

(4) (a) C. F. Wong, E. Auer, and R. T. LaLonde, *J. Org. Chem.*, **35**, 517 (1970); (b) I. Kawasaki, I. Kusumoto, and T. Kaneko, *Bull. Chem. Soc. Jap.*, **41**, 1264 (1968); (c) K. Oda and H. Koyama, *J. Chem. Soc. B*, 1450 (1970).

(5) (−)-Deoxynuphridine gives a negative plain curve in the 310–230-nm region.

(6) G. Opitz, H. Hellmann, and H. W. Schubert, *Justus Liebigs Ann. Chem.*, **623**, 117 (1959).

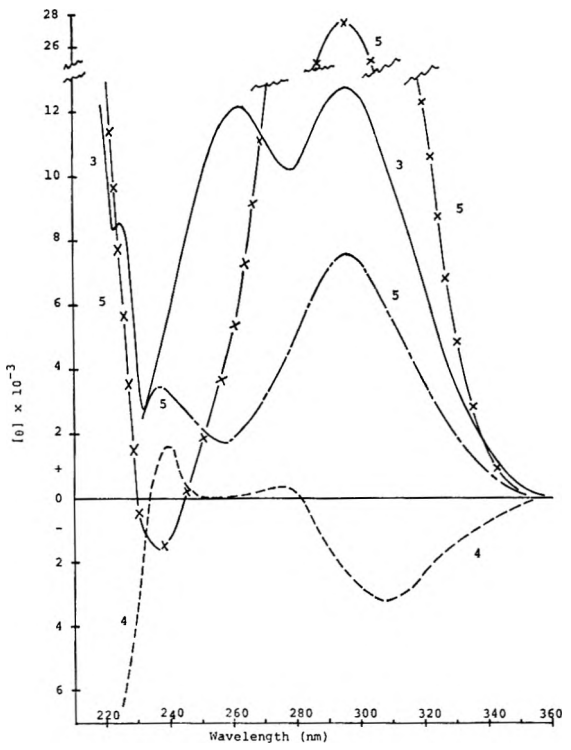


Figure 2.—The circular dichroism of immonium perchlorates derived from 6,6′-dihydroxythiobinupharidine (**3**) (—); 6,6′-dihydroxythionuphlutine B (**4**) (- - -); 6-hydroxythiobinupharidine (**5**) (- - -, in neutral EtOH), (- × -, in EtOH with added perchloric acid).

positive CD bands ($[\theta]^{25}_{296}$ 13,000, *c* 3.5 mg/5 ml and $[\theta]^{25}_{296}$ 7800, *c* 1.3 mg/1 ml, respectively), whereas the perchlorate of bishemiaminal **4** gives a negative CD band ($[\theta]^{25}_{308}$ −3200, *c* 1 mg/2 ml). Therefore, since the relative configurations of carbons 1, 4, and 10 in the C_{30} alkaloids and in (−)-deoxynupharidine were demonstrated to be the same but the configuration at C-7 to be variable,[2] the absolute configurations of chiral centers in the AB quinolizidine system of the C_{30} alkaloids are now known and are represented in the structures given. Reasonably the configurations of corresponding centers in AB and A′B′ quinolizidine ring systems would be the same judging from the near symmetrical (C_2) incorporation of two deoxynupharidine moieties into the C_{30} skeleton. However, this latter proposal is being checked experimentally by studies now in progress.

The appearance of positive CD bands at 275 nm for the perchlorate of **4** and at 265 nm for the perchlorate of **3** results from an A′B′ immonium ion. The CD bands in the 230–240-nm region evident in the CD of perchlorates of **4** and **5** possibly are due to the presence of α-ethoxyamines which are in equilibrium with immonium ions. These CD bands become more intense in dilute solution but disappear altogether, with simultaneous enhancement of the immonium ion bands, when several drops of perchloric acid are added. This is demonstrated in the case of **5** by the CD curve in Figure 2.

These results demonstrate that the CD of immonium ions holds considerable promise as a simple method for gaining stereochemical information. Since many immonium ions are naturally occurring in the form of hemiaminals and are readily available by oxidation of tertiary amines, the CD of immonium ions would appear to have special applicability to the study of alkaloid structure.

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Reversible Deuteration of 2,6-Dimethoxy-1,4-benzoquinone in Alkali

Summary: Base catalyzes rapid replacement by deuterium of the ring protons in 2,6-dimethoxy-1,4-benzoquinone in D_2O, establishing that nucleophilic addition of a hydroxyl ion to form an *o*-quinal structure is the primary step in alkaline decomposition of the quinone.

Sir: On treatment with alkali, quinones undergo rapid decomposition and polymerization to yield dark pigments of humus-like character.[1] Quinone percursors of humins arise in nature as fungal metabolites[2] or as products of biodegradation of plant lignins by fungal phenol oxidases.[3] One of the quinones frequently encountered as a product of fungal or enzymatic degradation of lignin[3] or lignin model compounds[3-5] is 2,6-dimethoxy-1,4-benzoquinone (**1**). This compound and its conversion products are therefore considered to be likely components of soil humus.

The rate of decomposition of unsubstituted *p*-benzoquinone in 0.1 *N* sodium hydroxide is so fast that special flow methods had to be applied in efforts to study the kinetics and course of the primary reaction.[6] However, the dimethoxy-*p*-benzoquinone (**1**) is relatively stable in alkali, where it undergoes unusual base-catalyzed exchange reactions which indicate that a nucleophilic addition of a hydroxyl ion onto the quinone must be the initial step in its alkaline decomposition.

The quinone **1** was prepared by nitric acid oxidation of 2,6-dimethoxyphenol[5] and purified by vacuum sublimation (mp 255°). Addition of alkali to a yellow aqueous solution of **1** [λ_{max} 289, 396 nm (ϵ 14,500, 660)] produced a colorless solution with only a single maximum at 249 nm (ϵ 15,300). On immediate reacidification, the original spectrum was regenerated and unchanged **1** could be recovered almost quantitatively from the solution by extraction with chloroform [λ_{max} (in $CHCl_3$) 286, 376 nm (ϵ 18,000, 600)].

A sample of **1** [pmr in $CDCl_3$, δ 3.82 (s, 2,6-OCH_3), 5.85 (s, 3,5-H)] was dissolved in alkaline D_2O and the solution acidified 1 min later with HCl in D_2O. The

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(4) W. J. Connors, J. S. Ayers, K. V. Sarkanen, and J. S. Gratzl, *Tappi*, **54**, 1248 (1971); (b) S. I. Clare and C. Steelink, *Tappi*, **56**, 119 (1973); (c) J. D. Fitzpatrick and C. Steelink, *J. Org. Chem.*, **37**, 762 (1972); (d) E. S. Caldwell and C. Steelink, *Biochim. Biophys. Acta*, **184**, 420 (1969); (e) T. K. Kirk, J. M. Harkin, and E. B. Cowling, *ibid.*, **165**, 145 (1968).

(5) W. Baker, *J. Chem. Soc.*, 622 (1941).

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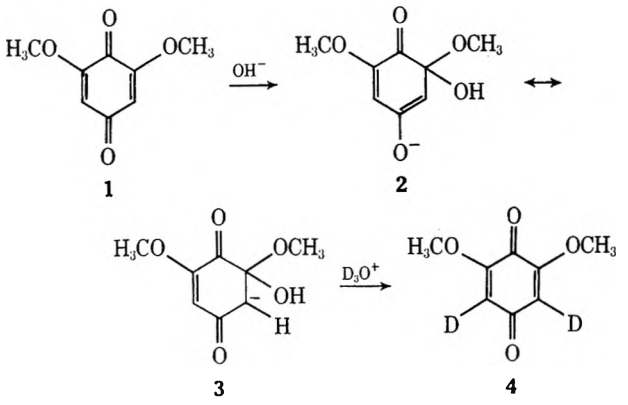
solution was extracted with chloroform, the extract dried, and the solvent removed. The pmr of the residue in $CDCl_3$ showed only a singlet at δ 3.82, indicating that the recovered product was 3,5-dideuterio-2,6-dimethoxy-1,4-benzoquinone (**4**).

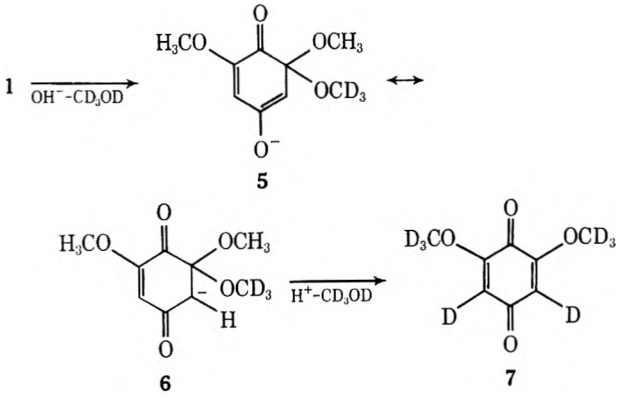
The formation of **4** can be explained as follows. In



alkaline solution, a hydroxyl ion adds on to **1** to yield an anion hitherto formulated as **2**;[4b,c,6] however, this is evidently tautomeric with the anion **3**, a form through which exchange of the ring protons can occur readily in D_2O *via* deuteration and deprotonation. Reacidification in D_2O therefore yields **4**. The original quinone **1** was re-formed from **4** by dissolution in NaOH–H_2O and acidification with HCl–H_2O. This rapid reversible deuteration therefore indicates the immediate formation in base of adducts of the type **2** ↔ **3**, which has been postulated as the first step in the alkaline decomposition of quinones.[4b,c,6]

Even for a substituted quinone, **1** is atypical in its relative stability in base. Its decomposition in alkali, as measured by the decay of the peak at 289 nm after reacidification, follows first-order kinetics with a half-life of 30 min at pH 10.5 and 20°. Other substituted quinones (1,2- and 1,4-naphthoquinone, 2-methyl-1,4-naphthoquinone, 2-methoxy-, 2,5-dimethyl-, 2,6-dimethyl-, 2,5-dichloro-, and 2,6-dichloro-1,4-benzoquinone, and 3,5-dimethoxy-1,2-benzoquinone) all decomposed within 1 min at pH 10.5. Regeneration of original quinones by acidification could not be established by uv or pmr spectroscopy. It was, therefore, impossible to establish deuterium exchange in alkaline solution.

On treatment of **1** with NaOH or CD_3ONa in CDCl–CD_3OD, both the methoxyl and proton resonances were immediately discharged from the pmr spectrum. 3,5-Dideuterio-2,6-bis(trideuteriomethoxy)-1,4-benzoquinone (**7**) recovered from the solution after acidification was



reconverted to **1** with NaOH in CH_3OH followed by acidification.

The exchange of the methoxyl probably involves an intermediate quinal (quinol ether) adduct (**6** ↔ **7**) analogous to the *o*-hemiquinal structure (**2** ↔ **3**). Rapid exchange of the methoxyl groups in **1** in alkaline solution by other alkoxyl groups has also been demonstrated by pmr and esr.[4c]

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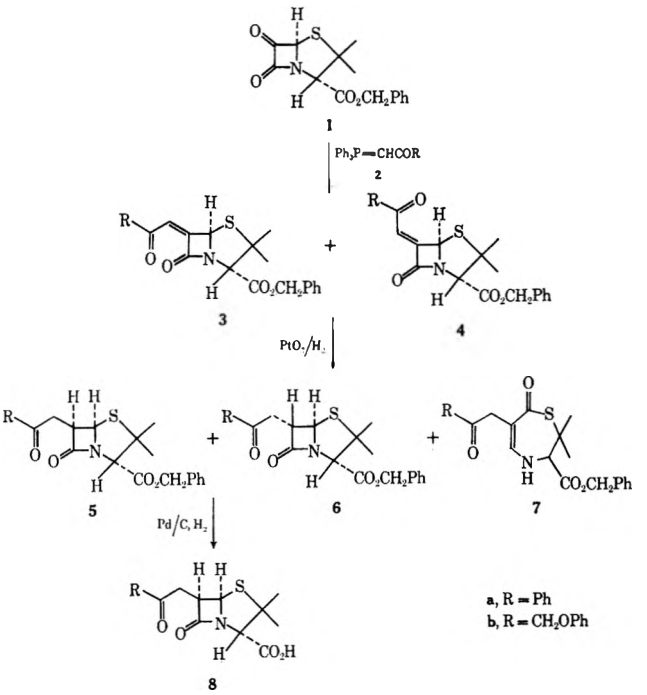
Benzyl 6-Oxopenicillanate and Derivatives. II

Summary: The amide side chain of a penicillin has been removed and the carbon analogs of penicillin V and phenylpenicillin have been synthesized stereospecifically; the penicillin V analog has antibiotic activity and penicillinase resistance.

Sir: We have reported[1] the preparation of 6β-phenoxyacetoxypenicillanic acid—a 6-oxygen analog of penicillin V, from benzyl 6-oxopenicillanate (**1**). This versatile



intermediate can also be transformed to 6β-phenoxyacetylmethylpenicillanic acid (**8b**)—a 6-carbon analog of penicillin V. Surprisingly, this relatively major change in structure resulted in a compound still containing appreciable antibiotic activity. In addition, **8b** was resistant to *Bacillus cereus* penicillinase.[2]

As a model side-chain precursor, the readily available benzoylmethylenetriphenylphosphorane (**2a**) was allowed to react with benzyl 6-oxopenicillanate (**1**) in refluxing benzene to give, after column chromatography, a yellow oily product (64%), benzyl benzoylmethylene-

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(2) Bristol Laboratories, Division of Bristol-Myers Co., Syracuse, N. Y. In the previous communication.[1] crude 6β-phenoxyacetoxypenicillanic acid was reported to be inactive. The potassium salt of this acid has since been retested and showed some antibacterial activity. Presumably the crude acid sample had decomposed before bioassay.

penicillanate:[3] R_f 0.75 (1:50 Et_2O–CH_2Cl_2); ir (film) 1770, 1740, 1690, 1635, 1595, 1450 cm^{-1}; nmr ($DCCl_3$) δ 8.07–7.30 ppm (m, 11 H), 6.12 (d, 1 H, J = 1 Hz), 5.22 (s, 2 H), 4.60 (s, 1 H), 1.60 (s, 3 H), 1.45 (s, 3 H). Presumably this oil was a mixture of the geometrical isomers **3a** and **4a**.

Hydrogenation of the oily benzyl benzoylmethylenepenicillanate in ethyl acetate in the presence of platinum oxide gave two fractions of oily products after column chromatography. The nmr spectrum of the major fraction (49%) provided good evidence for a mixture of *cis*- and *trans*-benzyl benzoylmethylpenicillanate (**5a** and **6a**). Column chromatography effected partial separation of the two epimers. An early fraction contained the cis and trans epimers in a 2:1 ratio, which increased to 19:3 in a later fraction. The overall cis:trans ratio was ~4:1. A sample containing the cis and trans epimers in a 2:1 ratio gave the following spectra: nmr ($DCCl_3$) δ 8.05–7.20 ppm (m, 30 H, aromatic protons), 5.70 (d, 2 H, J = 4.5 Hz, C-5 proton of the cis epimer), 5.20 (s, 6 H, benzylic protons), 5.10 (d, 1 H, J = 1.5 Hz, C-5 proton of the trans epimer), 4.52 (s, 1 H, C-3 proton of the trans epimer), 4.48 (s, 2 H, C-3 proton of the cis epimer), 4.30–3.25 (m, 9 H, C-6 protons and α protons to the ketone function), 1.60–1.40 (d over d, 18 H, *gem*-dimethyl protons); ir (film) 1770, 1740, 1680, 1600, 1450 cm^{-1}.

The minor portion [16%; ir (film) 3300, 1735, 1680, 1625, 1560–1500, 1200, 1000, 910 cm^{-1}; nmr ($DCCl_3$) δ 8.05–7.20 ppm (m, 10 H), 6.85–7.75 (d, 1 H, J = 8 Hz), 6.55–6.30 (m, 1 H, J = 5, 8 Hz), 5.15 (s, 2 H), 4.40–4.30 (d, 1 H, J = 5 Hz), 4.18–3.40 (q, 2 H, J = 17 Hz), 1.50 (s, 3 H), 1.40 (s, 3 H)] has tentatively been assigned the structure of 2,2-dimethyl-3-carbobenzyloxy-6-benzoylmethyl-7-oxo-2,3,4,7-tetrahydro-1,4-thiazepine (**7a**)[3] based on similar spectral data and the same nmr coupling pattern as the 1,4-thiazepine derivatives reported by Sjöberg, *et al.*,[4] and Clayton, *et al.*[5]

Condensation of phenoxyacetylmethylenetriphenylphosphorane (**2b**) with benzyl 6-oxopenicillanate (**1**) gave, after column chromatography, benzyl 6-phenoxyacetylmethylenepenicillanate[3] (62%) as a yellow oil: R_f 0.65 (1:25 Et_2O–CH_2Cl_2); ir (film) 1775, 1735, 1715, 1595, 1490 cm^{-1}; nmr ($DCCl_3$) δ 7.40–6.70 ppm (m, 11 H), 6.05 (d, 1 H, J = 1 Hz), 5.15 (s, 2 H), 4.70 (s, 2 H), 4.65 (s, 1 H), 1.55 (s, 3 H), 1.40 (s, 3 H). This oil may contain both geometrical isomers **3b** and **4b**.

Hydrogenation of benzyl 6-phenoxyacetylmethylenepenicillanate gave, after column chromatography, three product fractions. The first fraction contained a 29% yield of a mixture of the cis and trans epimers, **5b** and **6b**, in a 4:1 ratio. The second fraction contained the pure cis epimer **5b** in ~1% yield. The third fraction contained 2,2-dimethyl-3-carbobenzyloxy-6-phenoxyacetylmethyl-7-oxo-2,3,4,7-tetrahydro-1,4-thiazepine (**7b**, yield 7.5%). Benzyl 6β-phenoxyacetylmethylpenicillanate (**5b**)[3] was isolated as a pale yellow oil: R_f 0.75 (1:10 Et_2O–CH_2Cl_2); ir (film) 1770, 1735, 1595, 1490 cm^{-1}; nmr ($DCCl_3$) δ 7.50–6.80 ppm (m, 10 H), 5.65 (d, 1 H, J = 4.2 Hz), 5.20 (s, 2 H), 4.60 (s, 2 H), 4.45 (s, 1 H), 4.30–3.85 (m, 1 H), 3.25–3.12 (d, 2 H, J = 8 Hz), 1.58 (s, 3 H), 1.42 (s, 3 H).

The free acid, **8b**, was obtained by hydrogenating a 8:1 cis:trans mixture of benzyl 6-phenoxyacetylmethylpenicillanate in ethyl acetate in the presence of palladium on charcoal (10%) at 25° and 1 atm pressure. The acid, **8b**,[3] was purified by crystallization from benzene: yield 43%; mp 101.5–102°; ir (KBr) 3440, 1785, 1765, 1750, 1730, 1720, 1700, 1595, 1490, 1225 cm^{-1}; nmr ($DCCl_3$) δ 11.15 (s, 1 H), 7.50–6.85 (m, 5 H), 5.65 (d, 1 H, J = 4.5 Hz), 4.65 (s, 2 H), 4.50 (s, 1 H), 4.30–3.95 (m, 1 H), 3.35–3.20 (d, 2 H, J = 8 Hz), 1.65 (d, 6 H). Compound **8b** was found to be resistant to *Bacillus cereus* penicillinase and showed the following MIC's: *Diplococcus pneumoniae*, 1; *Streptococcus pyogenes*, 2; *Staphylococcus aureus* Smith, 32.

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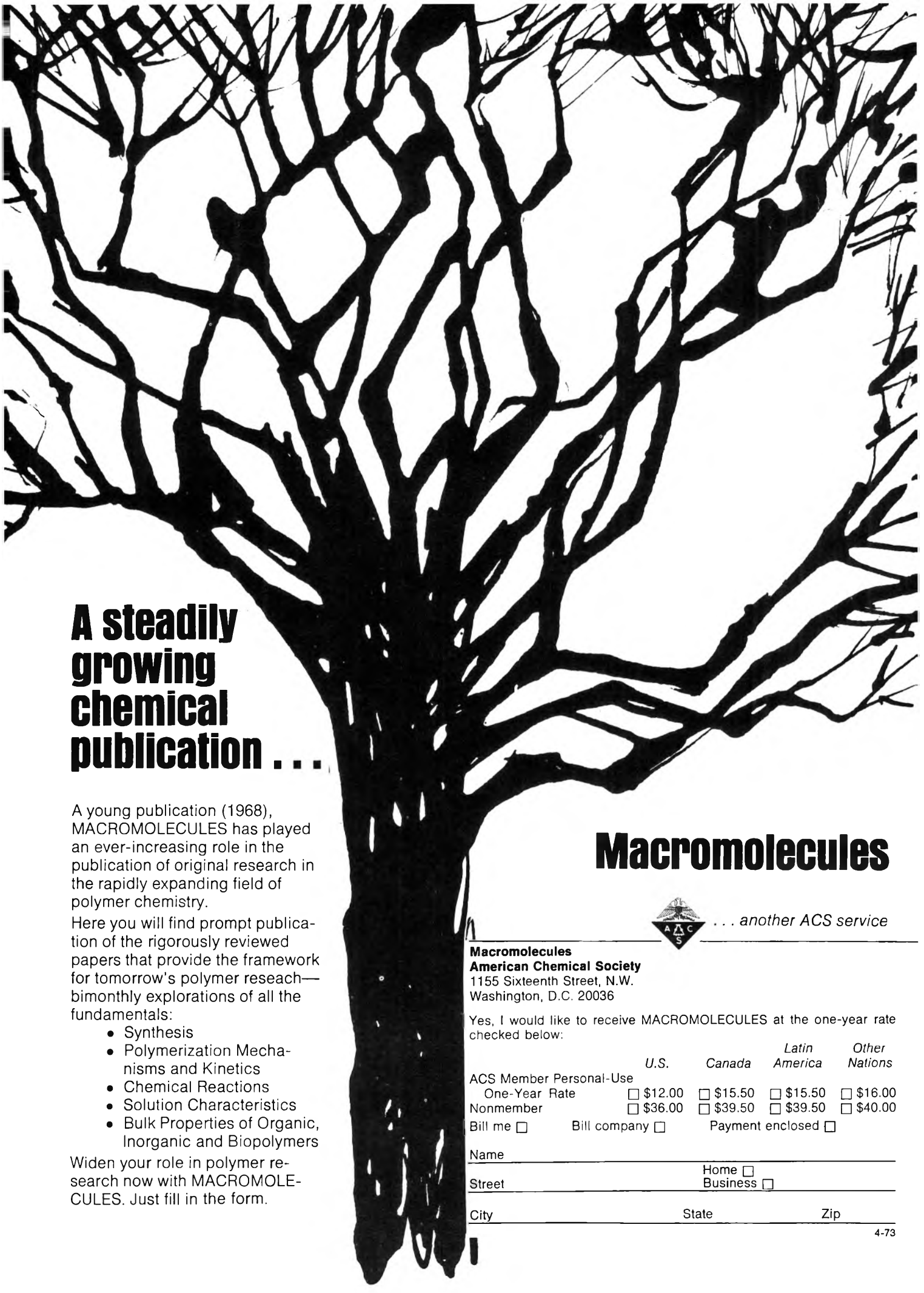

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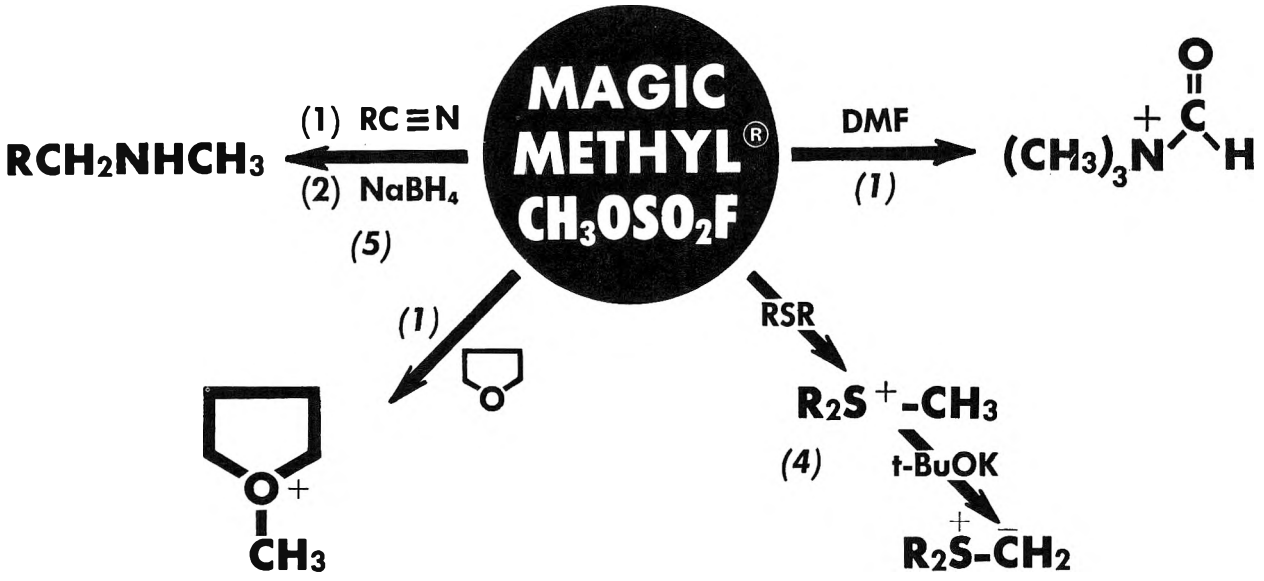

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