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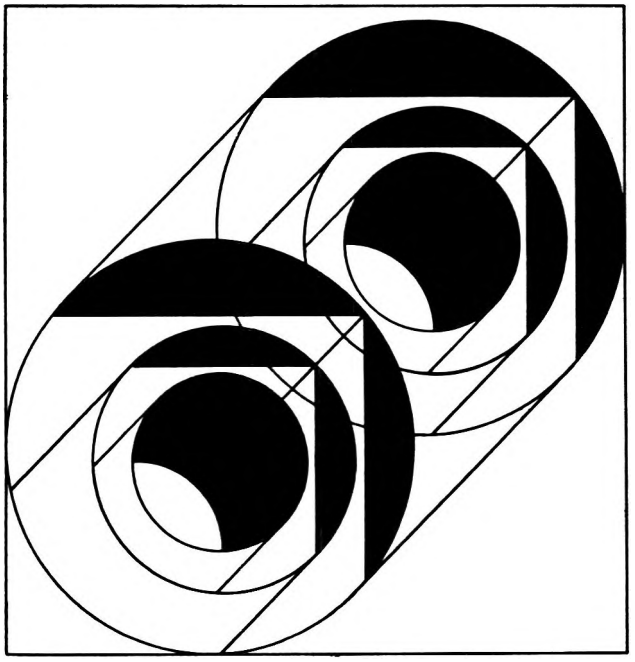

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THE JOURNAL OF Organic Chemistry®

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JULY 16, 1971

Bridged Polycyclic Compounds. LXVI. Electrophilic Additions to Dehydrojanusene and Related Reactions[1]

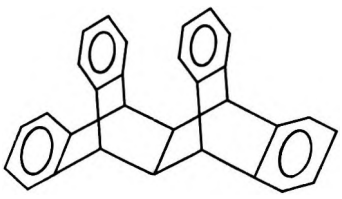
STANLEY J. CRISTOL* AND MICHAEL A. IMHOFF

Department of Chemistry, University of Colorado, Boulder, Colorado 80302

Received August 6, 1970

Electrophilic additions to dehydrojanusene (**2**) give mixtures of derivatives of janusenes (**10**) and of hemiisojanusenes (**11**), as do ring openings of epoxyjanusenes (**15**). Dehydrojanusene is compared in reactivity with dibenzobicyclo[2.2.2]octatriene (**9**) and its dimethyl derivative **16**.

The chemistry of the dibenzobicyclooctadiene systems has been of considerable interest to our research group for some time.[2-6] The stereochemistry of carbonium ion rearrangement attending addition or displacement reactions has commanded much attention, and recently we have been interested in reactions involving a novel polycyclic system, janusene (**1**).[7,8] We now wish to report the results of electrophilic additions to dehydrojanusene (**2**) which gives access to derivatives of janusene (**1**) and of several of its isomers (**3**, **4**, and **5**).



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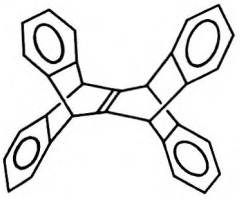

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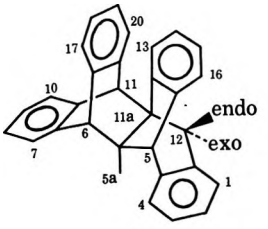
Nomenclature.—Because of the complexity of these polycyclic molecules, a trivial nomenclature has been developed. These compounds are formally described as derivatives of naphthacene, but the trivial nomenclature refers to them as relatives of janusene (**1**). For example, 5,5a,6,11,11a,12-hexahydro-5,11a:6,11-di-*o*-benzenonaphthacene (**3**) is termed hemiisojanusene. This compound can be imagined to arise from one Wagner–Meerwein rearrangement of the janusene skeleton. Compounds **4** (5,5a,6,11,11a,12-hexahydro-*cis*-5,11a:5a,11-di-*o*-benzenonaphthacene) and **5** (5,5a,6,11,11a,12-hexahydro-*trans*-5,11a:5a,11-di-*o*-benzenonaphthacene) are named *cis*-isojanusene and *trans*-isojanusene, respectively. These two compounds can be considered as arising from two Wagner–Meerwein rearrangements of the parent janusene system. The secondary benzylic positions of compounds **3**, **4**, and **5** are capable of exo



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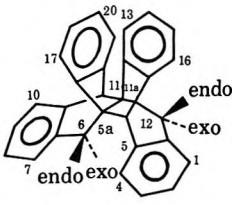

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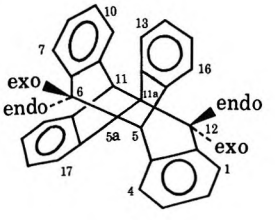


5

(quasiaxial) or endo (quasiequatorial) configuration, and the tertiary position at C-5a in **3** is always syn to the C-12 carbon atom.

Synthesis.—5,6,11,12-Tetrahydro-5,12:6,11-di-*o*-benzenonaphthacene (dehydrojanusene, **2**) was synthesized in 89% yields from the zinc debromination of 5a,11a-dibromojanusene (**6**).[9]

Electrophilic Additions.—Addition of hydrogen bromide and hydrogen chloride to methylene chloride solutions of dehydrojanusene gave only **7**-Br and **7**-Cl, respectively.[9] Addition of acetic acid to olefin **2** oc-

(1) Previous paper: LXV. S. J. Cristol and J. M. Sullivan, *J. Amer. Chem. Soc.*, **93**, 1967 (1971).

(2) S. J. Cristol, R. P. Arganbright, and D. D. Tanner, *J. Org. Chem.*, **28**, 1374 (1963).

(3) S. J. Cristol, J. R. Mohrig, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *J. Amer. Chem. Soc.*, **85**, 2675 (1963).

(4) S. J. Cristol and D. D. Tanner, *ibid.*, **86**, 3122 (1964).

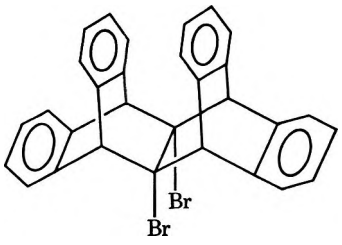
(5) S. J. Cristol, F. P. Parungo, and D. E. Plorde, *ibid.*, **87**, 2870 (1965).

(6) S. J. Cristol, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *ibid.*, **87**, 2879 (1965).

(7) S. J. Cristol and D. C. Lewis, *ibid.*, **89**, 1476 (1967).

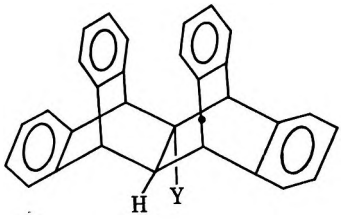
(8) S. J. Cristol and W. Y. Lim, *J. Org. Chem.*, **34**, 1 (1969).

(9) S. J. Cristol, M. A. Imhoff, and D. C. Lewis, *ibid.*, **35**, 1722 (1970).



6

curred readily to give only 7-OAc. At this point, we did not know whether to interpret these results as cis-concerted additions,[10] as cis additions involving an intermediate carbonium ion,[11] or as additions that gave initially the hemiisojanusene derivative **8**, which in



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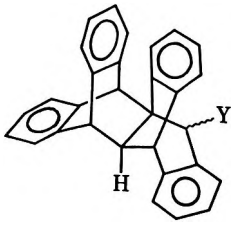

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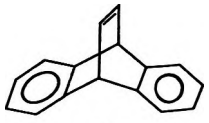
turn rearranged to **7** under the reaction conditions. This last mechanism seemed quite probable as dehydrojanusene can be viewed as a derivative of dibenzobicyclo[2.2.2]octatriene (**9**), which was known to undergo such rearrangements.[2-6]



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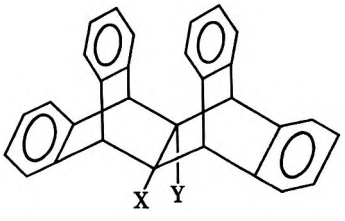
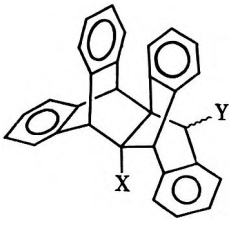
However, additions to dehydrojanusene involving electrophiles other than protonic species gave mixtures of janusene **10** and hemiisojanusene **11** derivatives (Table I). Most of the compounds of type **11** re-





10a, X = Cl; Y = Cl
b, X = Cl; Y = OAc
c, X = Cl; Y = OMe
d, X = Br; Y = OAc

11e, X = Br; Y = OMe
f, X = OH; Y = OAc
g, X = OH; Y = OMe

arranged to the janusene isomer **10** under acid catalysis[12] but were stable to the formation reaction conditions. The ratios of **10**:**11** observed were independent of the extent of reaction.

(10) R. C. Fahey in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Interscience, New York, N. Y., 1968, pp 237-342.

(11) (a) M. J. S. Dewar and R. C. Fahey, *J. Amer. Chem. Soc.*, **85**, 2245 (1963). (b) Trans addition to dehydrojanusene was not expected, as such an addition would involve very large steric strains.

(12) Dichloride **11a** rearranged to dichloride **10a** simply upon heating in carbon tetrachloride.

TABLE I

PRODUCT MIXTURES FROM ELECTROPHILIC ADDITIONS TO DEHYDROJANUSENE (2)

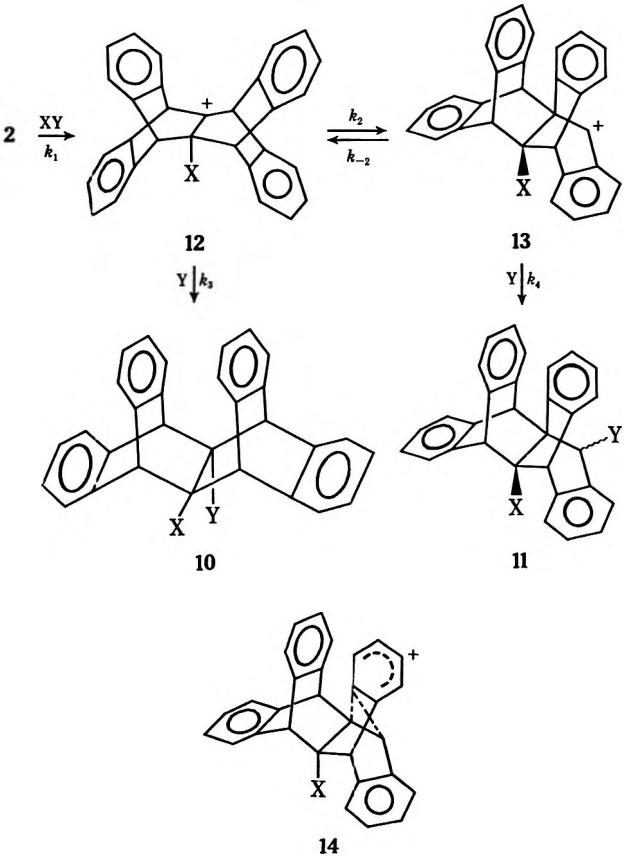
Reagents/substituents	X	Y	% 10	% 11[a]
Cl_2/CH_2Cl_2	Cl	Cl^-	20	80
tert-BuOCl/OAc^-–HOAc	Cl	HOAc	35	65
tert-BuOCl/MeOH	Cl	HOMe	60	40
NCS/MeOH	Cl	HOMe	60	40
NBS/OAc^-–HOAc	Br	HOAc	85	15
NBS/MeOH	Br	HOMe	100	0

[a] Product ratios were analyzed by pmr.

Compounds **10b** and **11b** were prepared by treatment with *tert*-butyl hypochlorite of a heterogeneous mixture of olefin **2** in a solution of sodium acetate in acetic acid. Similarly, the elements of acetyl hypobromite were added to olefin **2** to form **10d** and **11d** by using *N*-bromosuccinimide in acetic acid. Compounds **10c**, **11c**, and **10e** were formed from *tert*-butyl hypochlorite and *N*-bromosuccinimide, respectively, in methyl alcohol.

As noted in Table I, the product ratio (**10**:**11**) varied from 1:4 to 100:0 with differing electrophiles and nucleophiles. The results observed can be accommodated most simply as proceeding through the classical cations (Scheme I), **12** and **13**. Addition of an elec-

SCHEME I



trophile to dehydrojanusene (**2**) gives the tertiary cation **12**. This may rearrange to the secondary benzylic cation **13** or be trapped by a nucleophile (Y) to give the janusene derivative **10**. **13** may suffer analogous fates, that is, revert to **12** or give hemiisojanusene derivative **11**.

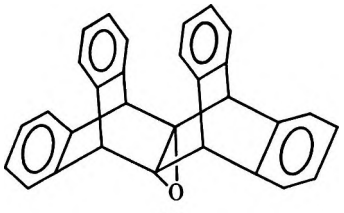
It is not possible, with the data presently available, to choose among the various alternatives for rationalizing the **10**:**11** product ratios observed. An attractive

explanation is that capture competes with rearrangement. This would explain the larger amount of **10** products in methanol as compared with acetic acid. This suggests that **12** and **13** are relatively stable compared with the transition state **14** separating them.[13] It is of interest that those cases where capture competes effectively with Wagner–Meerwein rearrangement often have tertiary classical cationic structures.[14] This explanation has the difficulty that the mixture formed by addition of chlorine is largely **11a**, while chloride ion is certainly a highly nucleophilic species[15] and is present as the gegenion in the ion pair formed directly from **2** and chlorine.

An alternative rationalization assumes that the **12** $\rightleftarrows$ **13** isomerization occurs readily and that the product mixture thus represents the result of $k_3[12]/k_4[13]$ or the equivalent k_3k_{-2}/k_4k_2. In such a situation our predictive capabilities are minimal; we cannot estimate either k_{-2}/k_2 (except to guess that it is likely to be within a few orders of magnitude of 10°) or k_3/k_4 for a given nucleophile. Winstein[16] has suggested that bidentate carbonium ions react with nucleophiles to give mixtures of products in a ratio which depends upon the nucleophilicity of the reagent. Thus, highly nucleophilic reagents tend to capture the ion at its more electron-deficient site (the transition state reflects the cationic structure), while less strong nucleophiles capture at the site reflecting product stability. It seems to us that the same kind of argument can be brought to bear upon a set of rapidly equilibrating cations, that is, upon a ratio analogous to k_3/k_4 for our system, but we are reluctant to apply this argument over the limited range of data we have available.

The effect of X on the rates of rearrangement and/or upon the ratio of **12**:**13** and the k_3:k_4 ratio also remains to be understood.

Of some interest with regard to the electrophilic additions discussed above were the reactions of 5a,11a-epoxyjanusene (**15**) with acetic acid and methyl



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alcohol. Opening of this epoxide with acetic acid gave a 3:1 mixture of hydroxyacetates **10f** and **11f**, respectively (Table II). Reaction of **15** with methyl alcohol[17] occurred slowly to give a 1:3 mixture of hydroxy methyl ethers **10g** and **11g**, respectively. Both **11f** and **11g** rearrange to **10f** and **10g**, respectively, under acid catalysis, but the data in Table II reflect kinetic control.

TABLE II

EPOXIDE RING OPENINGS OF 5a,11a-EPOXYJANUSENE (12)

Reagent	X	Y	% 10	% 11[a]
HOAc–OAc⁻	OH	OAc	75	25
HOAc	OH	OAc	75	25
MeOH	OH	OMe	25	75

[a] Product ratios were analyzed by pmr.

It is clear that both of these ring openings involve cationic intermediates **12**-OH and **13**-OH, and the data suggest that these are formed conjugate with an acetate ion in the acetic acid addition and with a methanol molecule in the reaction with methanol. It is not at all clear, with these assumptions, why so much **11** product is formed in the methanol case, as compared with the addition reactions to **2** in methanol, where the principal or sole products were **10** (see Table I).

Competition Reactions.—Inspection of molecular models of dehydrojanusene indicated that it might be an unreactive olefin for steric reasons. In order to obtain semiquantitative information with regard to the reactivity of **2**, we performed competitive addition reactions between **2** and 9,10-dihydro-9,10-ethenoanthracene (**9**). Olefin **9** was selected as a model which should have nearly the same characteristics of **2** with respect to bond strain but should not be sterically hindered. Also the chemistry of **9** was well understood. However, a complication was introduced in these comparisons, because **2** was tetrasubstituted but **9** was disubstituted. The results, which are summarized in Table III, indicate that dehydrojanusene (**2**) was more

TABLE III

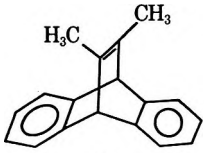
COMPETITIVE REACTIVITIES OF OLEFINS TOWARD ELECTROPHILIC REAGENTS

Substrates	Reagent	k_2/k_m[a]
2 and **9**	Br_2–CH_2Cl_2	1.5
2 and **9**	*m*-$ClC_6H_4CO_3H$	20
2 and **16**	*m*-$ClC_6H_4CO_3H$	0.05

[a] Product ratios were analyzed by pmr; k_m is the rate of the model compound.

reactive than model olefin **9**. This must be attributed to electronic effects. These results indicate only that the steric effects, if any, are not more important than the electronic effects in this system.

A competitive epoxidation between **2** and a tetrasubstituted model compound, 11,12-dimethyl-9,10-dihydro-9,10-ethenoanthracene (**16**), showed that there



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may be some steric hindrance to addition in **2**. Therefore, dehydrojanusene is a typical tetrasubstituted olefin that is only slightly deactivated due to steric hindrance.

(13) Structure **14** cannot represent the intermediate leading to products **11**, as both endo and exo epimers are formed, and we have therefore used it to represent a transition state.

(14) (a) J. D. Roberts and J. A. Yancey, *J. Amer. Chem. Soc.*, **77**, 5558 (1955); (b) H. C. Brown and C. J. Kim, *ibid.*, **90**, 2082 (1968); (c) H. L. Goering and K. Humski, *ibid.*, **90**, 6213 (1968). For examples of secondary systems, see (d) K. Takeuchi, T. Oshika, and Y. Koga, *Bull. Chem. Soc. Jap.*, **38**, 1318 (1965), and G. Fusco, Ph.D. Thesis, University of Colorado, 1965.

(15) For references, see S. J. Cristol and J. M. Sullivan, *J. Amer. Chem. Soc.*, **93**, 1967 (1971).

(16) A. Diaz, M. Brookhart, and S. Winstein, *ibid.*, **88**, 3133 (1966).

(17) Ring opening was not observed in methyl alcohol when sodium methoxide was present. It seems reasonable, therefore, to assume that the ring opening was catalyzed by adventitiously present acid.

Experimental Section

All proton magnetic resonance spectra were taken on a Varian A-60A instrument as saturated solutions in chloroform-d_1, using tetramethylsilane as an internal standard. All chemical shifts are reported in τ units (τ = 10.00 for tetramethylsilane). Infrared spectra were taken on a Beckman IR-5 spectrophotometer in either carbon tetrachloride or potassium bromide. All elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were uncorrected. Structure assignments are given in the third paper of this group.

Preparation of Dehydrojanusene (2).—A solution of 9.9 g (18.3 mmol) of dibromide 6[9] in 400 ml of DMSO was treated with 18 g of zinc which had been washed with 2% cupric sulfate solution until the blue color persisted. This mixture was stirred at 60° for 12 hr. It was filtered into 400 ml of water and the zinc residue was washed with 300 ml of CH_2Cl_2 and filtered. The precipitate in water was extracted with 300 ml of CH_2Cl_2 and this extract was combined with the filtrate from the zinc residue washings. The CH_2Cl_2 solution was washed seven times with 400-ml portions of water and dried ($MgSO_4$). The mixture was filtered and the solvent evaporated, yielding 6.17 g (89%) of dehydrojanusene (2). Recrystallization was from CH_2Cl_2–CCl_4: mp 360–361° dec; ν_{max} 1470, 1450, 1232, 1173, 1148, 1022, 926, 783, 749, 729, 637 cm^{-1} (KBr); pmr ($CDCl_3$) τ 4.84 (s, 4), 3.05 (m, 16, aromatics).

Anal. Calcd for $C_{30}H_{20}$: C, 94.70; H, 5.30. Found: C, 94.73; H, 5.21.

Addition of Acetic Acid to Dehydrojanusene (2).—To a solution of 82 mg (1.00 mmol) of sodium acetate in 40 ml of acetic acid was added 52 mg (0.14 mmol) of 2. The heterogeneous mixture was stirred and heated at 100° for 15.5 hr, during which time 2 went into solution. The chilled mixture was poured into 100 ml of water and extracted with 150 ml of ether. The ether extract was washed five times with 150-ml portions of water and once with 100 ml of saturated NaCl solution. The ether solution was dried ($MgSO_4$) and filtered and the solvent evaporated under reduced pressure, yielding 60 mg (95%) of 5a-acetoxyjanusene (7-OAc): mp (after recrystallization from methanol) 236–237°; pmr ($CDCl_3$) τ 8.52 (s, 3, OAc), 7.58 (t, 1, J = 2.5 Hz), 5.74 (d, 2, J = 2.5 Hz), 4.59 (s, 2), 2.80–3.40 (m, 16, aromatics).

Anal. Calcd for $C_{32}H_{24}O_2$: C, 87.27; H, 5.45. Found: C, 87.14; H, 5.43.

Addition of Chlorine to 2.—To a solution of 312 mg (0.82 mmol) of 2 in 50 ml of CH_2Cl_2 at −78° was added 3 mmol of chlorine. The solvent was evaporated under reduced pressure at 0°, giving 348 mg (94%) of a colorless oil. The pmr spectrum of this oil identified it as a mixture of 20% 5a,11a-dichlorojanusene (10a) and 80% 5a,12-dichlorohemiisojanusene (11a). Attempts to fractionally crystallize 11a in CCl_4 only caused it to rearrange to dichloride 10a. Crystalline 11a was never obtained and 11a could not be isolated in absence of 10a. Therefore, an elemental analysis of 11a was not obtained. Crystallization of dichloride 10a was from acetone–95% EtOH: mp 294–295° dec; pmr ($CDCl_3$) of 10a τ 5.35 (s, 4), 2.90–3.30 (m, 16, aromatics).

Anal. Calcd for $C_{30}H_{20}Cl_2$: C, 79.82; H, 4.43. Found: C, 79.62; H, 4.58.

The pmr ($CDCl_3$) of 11a showed τ 4.33 and 4.44 (s, 1), 4.89 and 5.01 (s, 1), 5.35 (s, 1), 5.58 (s, 1), 2.37–3.40 (m, 16, aromatics). Small absorptions at τ 4.44 and 4.89 were attributed to an epimer.

Reaction of *tert*-Butyl Hypochlorite in Acetic Acid with 2.—To a mixture of 1.00 g (2.63 mmol) of 2 and 390 mg (4.74 mmol) of sodium acetate in 60 ml of acetic acid was added 0.30 ml (2.7 mmol) of *tert*-butyl hypochlorite. The addition was performed over a 30-min period, and the reaction was stirred at room temperature in the dark for 2 hr. The small amount of unreacted olefin 2 which was still present was filtered, and the filtrate was dissolved in 200 ml of ether. The ether solution was washed five times with 200-ml portions of water and once with 200 ml of saturated NaCl solution. The solution was dried ($MgSO_4$) and filtered and the solvent evaporated under reduced pressure, yielding 1.17 g (94%) of acetoxy chlorides 10b and 11b, respectively. The two acetoxy chlorides were separated by fractional crystallization from benzene–heptane.

5a-Chloro-11a-acetoxyjanusene (10b) was recrystallized from benzene–heptane: mp 270–272°; pmr ($CDCl_3$) τ 8.34 (s, 3, OAc), 5.36 (s, 2), 4.49 (s, 2), 2.94–3.33 (m, 16, aromatics).

Anal. Calcd for $C_{32}H_{23}O_2Cl$: C, 80.93; H, 4.85. Found: C, 80.85; H, 4.96.

Recrystallization of 5a-chloro-12-acetoxyhemiisojanusene (11b) was also from benzene–heptane, mp 227–230°. This compound resolidified at about 235° and then melted with decomposition at 285°. It is believed that 11b rearranged to another acetoxy chloride upon melting: pmr ($CDCl_3$) τ 7.96 (s, 3, OAc), 5.57 (s, 1), 5.35 (s, 1), 4.97 (s, 1), 3.48 (s, 1) 2.95 (m, 16, aromatics).

Anal. Calcd for $C_{32}H_{23}O_2Cl$: C, 80.93; H, 4.85. Found: C, 80.69; H, 4.94.

Reaction of *tert*-Butyl Hypochlorite in Methanol with 2.—To a mixture of 71 mg (0.19 mmol) of 2 in 9 ml of methanol was added 3.3 ml of 0.09 *M* *tert*-butyl hypochlorite in methyl alcohol. The mixture was stirred at gentle reflux for 13 hr in the dark and then cooled for 2 hr. The unreacted olefin 2 was filtered and the filtrate dissolved in 80 ml of ether. The ether solution was worked up as described previously and yielded 34 mg of an oil which was identified by pmr as 60% 5a-chloro-11a-methoxyjanusene (10c) and 40% 5a-chloro-12-methoxyhemiisojanusene (11c). Chloromethyl ether 11c could not be isolated pure, but 10c was separated *via* thin layer chromatography and was crystallized from benzene–heptane: mp 300–303° dec; pmr ($CDCl_3$) of 10c τ 6.56 (s, 3, OMe), 5.38 (s, 2), 5.31 (s, 2), 2.97–3.33 (m, 16, aromatics).

Anal. Calcd for $C_{31}H_{23}OCl$: C, 83.31; H, 5.15. Found: C, 83.19; H, 5.23.

The pmr ($CDCl_3$) of 11c showed τ 6.07 (s, 3, OMe), 5.64 (s, 1), 5.36 (s, 1), 5.27 (s, 1), 5.06 (s, 1), 2.95 (m, 16, aromatics).

Reaction of *N*-Chlorosuccinimide in Methanol with 2.—A mixture of 62 mg (0.16 mmol) of 2 and 30 mg (0.22 mmol) of NCS was diluted with 35 ml of methanol and stirred at gentle reflux for 5 hr. Work-up gave 60 mg (85%) of a 3:2 mixture of chloromethyl ethers 10c and 11c, respectively.

Reaction of *N*-Bromosuccinimide in Acetic Acid with 2.—A mixture of 326 mg (0.86 mmol) of 2, 376 mg (4.58 mmol) of sodium acetate, and 182 mg (1.02 mmol) of NBS was partially dissolved in 45 ml of acetic acid. This mixture was stirred in the dark at room temperature for 30 hr. The reaction mixture was poured into 100 ml of ether and washed five times with 150-ml portions of water. The ether solution was dried ($MgSO_4$) and filtered, and the solvent evaporated under reduced pressure yielding 378 mg (85%) of a 85:15 mixture of 5a-bromo-11a-acetoxyjanusene (10d) and 5a-bromo-12-acetoxyhemiisojanusene (11d), respectively. Acetoxy bromide 11d could not be isolated pure. Acetoxy bromide 10d was crystallized from benzene–heptane: mp 259–260.5°; pmr ($CDCl_3$) τ 8.32 (s, 3, OAc), 5.13 (s, 2), 4.52 (s, 2), 2.94–3.28 (m, 16, aromatics).

Anal. Calcd for $C_{32}H_{23}O_2Br$: C, 73.99; H, 4.43. Found: C, 73.87; H, 4.43.

The pmr ($CDCl_3$) of 11d showed τ 7.97 (s, 3, OAc), 5.45 (s, 1), 5.17 (s, 1), 4.97 (s, 1), 2.95 (m, 16, aromatics).

Reaction of *N*-Bromosuccinimide in Methanol with 2.—A mixture of 62 mg (0.16 mmol) of 2 and 40 mg (0.22 mmol) of NBS, diluted in 40 ml of methanol, was stirred at room temperature in the dark for 6.5 hr. The mixture was worked up as described previously, yielding 80 mg (100%) of 5a-bromo-11a-methoxyjanusene (10e) and no 11e. Crystallization of 10e was from benzene–heptane: mp 284–285° dec; pmr ($CDCl_3$) τ 6.53 (s, 3, OMe), 5.31 (s, 2), 5.17 (s, 2), 2.95–3.35 (m, 16, aromatics).

Anal. Calcd for $C_{31}H_{23}OBr$: C, 75.76; H, 4.68. Found: C, 75.63; H, 4.71.

Preparation of 5a,11a-Epoxyjanusene (15).—To a solution of 603 mg (1.59 mmol) of 2 in 30 ml of CH_2Cl_2 was added 341 mg (1.59 mmol) of 85% pure *m*-chloroperbenzoic acid dissolved in 25 ml of CH_2Cl_2. This mixture was stirred in the dark at room temperature for 65 hr. The reaction was worked up by washing twice with ferrous ammonium sulfate solution, twice with 10% Na_2CO_3 solution, and twice with 150-ml portions of water. The mixture was dried ($MgSO_4$) and filtered, and the solvent evaporated under reduced pressure yielding 452 mg (72%) of 5a,11a-epoxyjanusene (15). Crystallization of 15 was from benzene–heptane: mp 283–285° dec; pmr ($CDCl_3$) τ 5.32 (s, 4), 3.35 (m, 4, aromatics), 2.96 (m, 12, aromatics).

Anal. Calcd for $C_{30}H_{20}O$: C, 90.91; H, 5.05. Found: C, 90.82; H, 4.98.

Reaction of 5a,11a-Epoxyjanusene (15) with Sodium Acetate and Acetic Acid.—A mixture of 78 mg (0.20 mmol) of 15 and 88 mg (1.07 mmol) of sodium acetate in 15 ml of acetic acid was stirred at room temperature for 34 hr and then poured into 100

ml of water. The precipitate was extracted with 100 ml of ether which was then washed six times with 150-ml portions of water and once with 100 ml of saturated NaCl solution. The mixture was dried ($MgSO_4$) and filtered and the solvent evaporated under reduced pressure yielding 76 mg of an oil, which was identified by pmr as 15% unreacted **15**, 64% 5a-hydroxy-11a-acetoxyjanusene (**10f**), and 21% 5a-hydroxy-12-acetoxyhemiisojanusene (**11f**). The hydroxyacetates were in a ratio of 3:1, respectively.

Compound **10f** was crystallized from MeOH: mp 280–284°; pmr ($CDCl_3$) τ 8.38 (s, 3, OAc), 5.56 (s, 2), 4.53 (s, 2), 2.96–3.31 (m, 16, aromatics).

Anal. Calcd for $C_{32}H_{24}O_3$: C, 84.21; H, 5.26. Found: C, 84.09; H, 5.34.

Compound **11f** was prepared by another route which will be reported later.[18]

Reaction of 5a,11a-Epoxyjanusene (15) with Acetic Acid.—A solution of 64 mg (0.16 mmol) of **15** in 10 ml of acetic acid was stirred at room temperature for 19 hr. The mixture was then worked up as described above. The pmr spectrum of the mixture showed 22% unreacted epoxide **15**, 56% hydroxyacetate **10f** and 22% hydroxyacetate **11f**. The last two compounds were in a ratio of 3:1, respectively.

Reaction of 5a,11a-Epoxyjanusene (15) with Methanol.—A solution of 60 mg (0.15 mmol) of **15** in 15 ml of "spectro-grade" methanol was stirred at gentle reflux for 18 hr. The solvent was then evaporated under reduced pressure yielding 62 mg (100%) of a mixture of 25% 5a-hydroxy-11a-methoxyjanusene (**10g**) and 75% 5a-hydroxy-12-methoxyhemiisojanusene (**11g**). These two compounds were separated by fractional crystallization from benzene–heptane.

From benzene–heptane **10g** was crystallized: mp 325–327° dec; pmr ($CDCl_3$) τ 6.65 (s, 3, OMe), 5.57 (s, 2), 5.34 (s, 2), 2.95–3.35 (m, 16, aromatics).

Anal. Calcd for $C_{31}H_{24}O_2$: C, 86.92; H, 5.61. Found: C, 86.81; H, 5.67.

From benzene–heptane **11g** was also recrystallized: mp 257.5–259°; pmr ($CDCl_3$) τ 6.26 (s, 3, OMe), 5.76 (s, 1), 5.41 (s, 1), 5.26 (s, 1), 5.10 (s, 1), 2.9 (m, 16, aromatics).

Anal. Calcd for $C_{31}H_{24}O_2$: C, 86.92; H, 5.61. Found: C, 86.70; H, 5.79.

Reaction of 5a,11a-Epoxyjanusene (15) with Sodium Methoxide and Methanol.—A mixture of 58 mg (0.15 mmol) of **15** in 15 ml of 0.5 *M* sodium methoxide in methanol solution was stirred at reflux for 17 hr. The mixture was then poured into ether and worked up as previously described. The isolated material was identified by its pmr spectrum as 5a,11a-epoxyjanusene (**15**). This was the only product detected.

Competitive Addition of Bromine to 9,10-Dihydro-9,10-ethenoanthracene (9) and 2.—A mixture of 435 mg (2.13 mmol) of **9** and 199 mg (0.53 mmol) of **2** was dissolved in 50 ml of CH_2Cl_2. To this solution was added 3 ml of 0.18 *M* bromine–methylene chloride solution, and, although the reaction mixture became colorless immediately, it was stirred for a few hours. The solvent was then evaporated under reduced pressure and a pmr spectrum of the mixture indicated a 3:1 mixture of 4-*syn*-8-dibromodibenzobicyclo[3.2.1]octadiene[19] and 5a,11a-dibromojanusene (**6**), respectively. **6** is relatively insoluble, and the difficulty of obtaining a homogeneous pmr sample suggests that this ratio of yields of products was lower than 3.

Competitive Epoxidation of 9,10-Dihydro-9,10-ethenoanthracene (9) and Dehydrojanusene (2).—A mixture of 80 mg (0.39 mmol) of **9** and 150 mg (0.39 mmol) of **2** was dissolved in 35 ml of CH_2Cl_2. To this solution was added 44 mg (0.22 mmol) of 85% pure *m*-chloroperbenzoic acid in 10 ml of CH_2Cl_2. The reaction was stirred at room temperature in the dark for 75 hr. The reaction mixture was worked up by simply evaporating the solvent under reduced pressure. The heterogeneous pmr sample of the product mixture showed only unreacted **9**, epoxide **15**, and a trace of *m*-chlorobenzoic acid. The product from epoxidation of **9**[20] was not detected in the pmr sample. It would surely have been soluble in $CDCl_3$ and therefore detected. If it is assumed that the pmr method of analysis was good to 5%, the rate of epoxidation of **2** must be at least 20 times that of **9**.

Competitive Epoxidation of 11,12-Dimethyl-9,10-dihydro-9,10-ethenoanthracene (16)[21] and Dehydrojanusene (2).—A mixture of 120 mg (0.52 mmol) of **16**, 198 mg (0.52 mmol) of **2**, and 12 mg (0.07 mmol) of *p*-dinitrobenzene (internal standard) was dissolved in 30 ml of CH_2Cl_2. To this solution was added 53 mg (0.26 mmol) of 85% pure *m*-chloroperbenzoic acid in 10 ml of CH_2Cl_2. The reaction mixture was stirred in the dark at room temperature for 61 hr, after which it was worked up as described above. The pmr spectrum of the heterogeneous sample (dehydrojanusene was insoluble) showed unreacted olefin **16**, 11,12-epoxy-11,12-dimethyl-9,10-dihydro-9,10-ethanoanthracene, and a trace of epoxide **15**. The presence of epoxide **15** was confirmed by developing a sample of the product mixture on a thin layer plate with 5% ether–benzene. It was assumed that the trace of epoxide represented 5% of the product.

Registry No.—**2**, 29309-28-2; **7**-OAc, 29309-29-3; **10a**, 29309-30-6; **10b**, 29309-31-7; **10c**, 29308-18-7; **10d**, 29308-17-6; **10e**, 29309-34-0; **10f**, 29308-22-3; **10g**, 29308-21-2; **11a**, 29309-37-3; **11b**, 29308-24-5; **11c**, 29308-25-6; **11d**, 29308-30-3; **11g**, 29308-26-7; **15**, 29308-23-4.

Acknowledgments.—The authors are indebted to the National Science Foundation and to the Institute of General Medical Sciences (Public Health Service Grant GM-12139) for support of this work.

(18) S. J. Cristol and M. A. Imhoff, *J. Org. Chem.*, **36**, 1854 (1971).

(19) S. J. Cristol, J. R. Mohrig, and D. E. Plorde, *ibid.*, **30**, 1956 (1965).

(20) S. J. Cristol and R. K. Bly, *J. Amer. Chem. Soc.*, **82**, 6155 (1960).

(21) The chemistry of **16** and related systems will be reported later by Hans Mueller.

Bridged Polycyclic Compounds. LXVII. Carbonium Ion Rearrangements among Janusene, Hemiisojanusene, and Isojanusene Derivatives[1]

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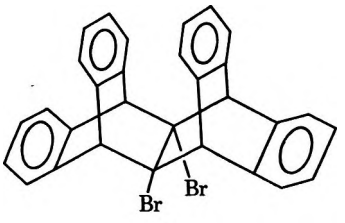
Carbonium ion rearrangements accompanying solvolysis were studied among janusene, hemiisojanusene, and *cis*- and *trans*-isojanusene compounds, using methods of kinetic and thermodynamic control. Plausible reaction schemes for these interconversions are discussed.

In the course of our work on the chemistry of janusene[2] and its derivatives and relatives,[1] we decided to look at carbonium ion rearrangements of the individual bicyclic systems. The availability of 5a,11a-dibromojanusene (**1**)[3,4] and of 5a,12-dichlorohemiisojanusene (**2**)[1,4] made entrée into this problem *via* silver-assisted solvolyses simple, even though the high reactivity of both halogen atoms in each compound made it impossible to do selective monoacetolyses.



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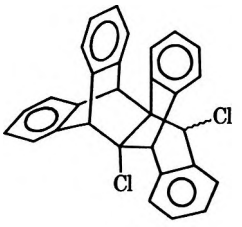

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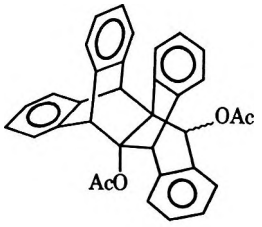

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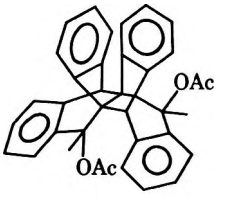
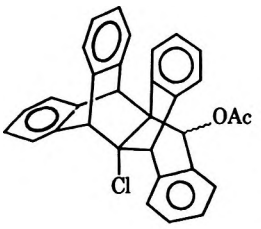


4

Treatment of dibromide **1** with 2 equiv of silver acetate gave an 85:15 ratio of diacetates **3** and **4**, respectively. On the other hand, dichloride **2** reacted with 2 equiv of silver acetate to give a 30:70 ratio of diacetates **3** and **4**, respectively. Although the intermediate acetoxy chlorides could not be obtained readily by treating dichloride **2** with 1 equiv of silver acetate, they were readily prepared by treating dehydrojanusene with *tert*-butyl hypochlorite in acetic acid.[1] This gave a 65:35 ratio of 5a-chloro-12-acetoxyhemiisojanusene (**5**) and 5a-chloro-11a-acetoxyjanusene (**6**), respectively. These acetoxy chlorides could be separated by fractional crystallization.

Acetoxy chloride **5**, which was a 4:1 mixture of epimers, rearranged readily in 0.1 *M* perchloric–acetic acid at room temperature in 1 hr to acetoxy chloride **6**. During the rearrangement the epimer composition of **5** did not change. Acetoxy chloride **6** was quite



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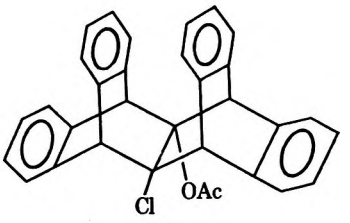
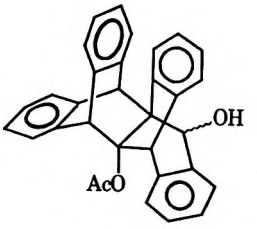


6

stable. Even 1.1 *M* sulfuric acid in methanol at reflux for 142 hr gave only unreacted starting material.

Silver-assisted acetolysis of 5a-chloro-11a-acetoxyjanusene (**6**) gave only 5a,12-diacetoxyhemiisojanusene (**3**). This same reaction in wet acetic acid gave diacetate **3** along with 5a-acetoxy-12-hydroxyhemiisojanusene (**7**). The absence of hydroxyacetate **8** from this last experiment excluded acetoxonium ion **9** as an



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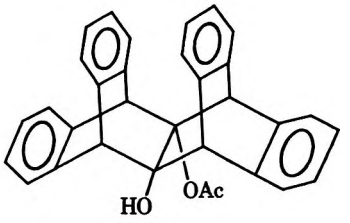

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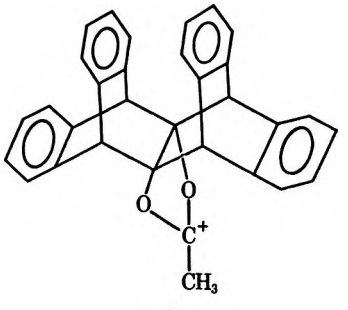

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intermediate in this solvolysis.[5,6] Similar treatment of 5a-bromo-11a-acetoxyjanusene (**10**)[1] gave identical results.

These results are interpreted in Scheme I. Ions **11** and **12** are analogous to those observed in the electrophilic additions to dehydrojanusene.[1] A phenonium ion could be introduced into this scheme,[7] but at present we have no direct evidence for it as a product-forming intermediate. Cis-disubstituted products (re-

(1) Previous paper: LXVI. S. J. Cristol and M. A. Imhoff, *J. Org. Chem.*, **36**, 1849 (1971).

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

(3) S. J. Cristol, M. A. Imhoff, and D. C. Lewis, *J. Org. Chem.*, **35**, 1722 (1970).

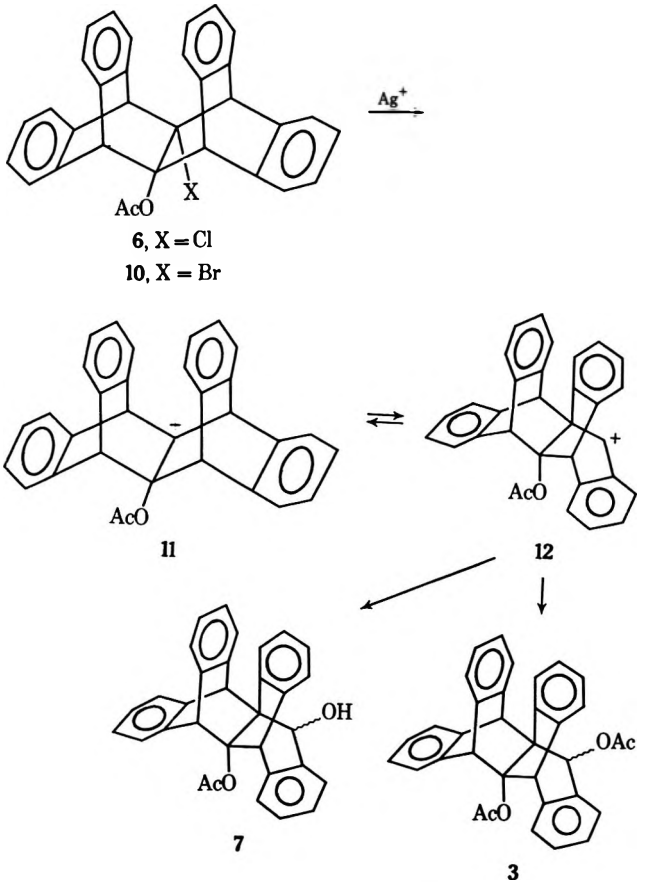
(4) The naming of compounds in this paper follows the procedure described in the previous paper (ref 1).

(5) S. J. Cristol, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *J. Amer. Chem. Soc.*, **87**, 2879 (1965).

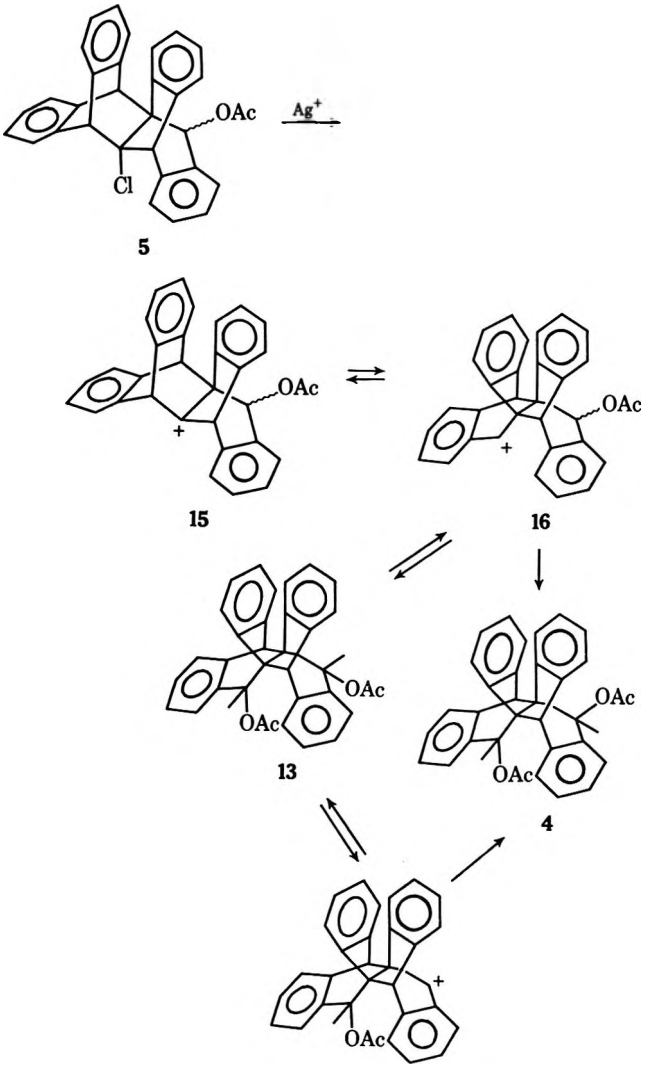
(6) R. M. Roberts, J. Corse, R. Boschan, D. Seymour, and S. Winstein, *ibid.*, **80**, 1247 (1958).

(7) Such an ion must obviously intervene in the rearrangement of **11** ⇄ **12**.

SCHEME I

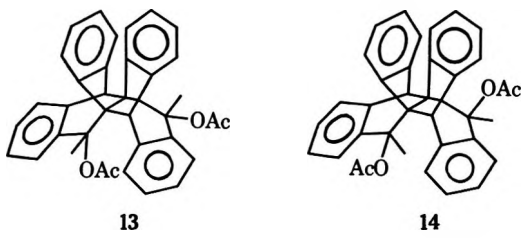


SCHEME II



sulting from intermediate **11**) were not formed (within the limits of our analysis), although such products are formed in many addition reactions. A possible explanation for the absence of products from intermediate **11** is that rotation of the acetoxy group hinders attack by nucleophiles at C-11a. In other words, the "windshield wiper" effect of this substituent sweeps away nucleophiles from the reactive site. Thus, the intermediates are trapped as diacetate **3** or hydroxyacetate **7**, which were shown to be stable to the reaction conditions. These results revealed the source of diacetate **3** in the initial solvolyses as acetoxy halides **6** and **10**.

Treatment of 5a-chloro-12-acetoxyhemiisojanusene (**5**), which was a 1:4 epimeric mixture, with silver acetate in acetic acid for 2 min (75% reaction) gave a 1:4 mixture of *exo*-6,*exo*-12-diacetoxy-*cis*-isojanusene (**13**) and *exo*-6,*endo*-12-diacetoxy-*cis*-isojanusene (**4**),



respectively. After being allowed to stand in acetic acid for 30 min, **13** epimerized to **4**. Diacetate **4** was shown to be stable to the reaction conditions and did not epimerize to the corresponding "diendo" compound **14**. This latter diacetate was observed in subsequent reactions and will be discussed later. These results can be most simply explained in terms of exo attack on ion **16** (Scheme II). The dominant epimer of acetoxy chloride **5** would thus appear to be the endo one since the ratio of epimers was constant during its acid-catalyzed rearrangement to **6** and because **4** is assumed to be a kinetic product along with **13**. There is no evidence in these results for or against the existence of ion **15** since it was not trapped (diacetate **3** would have been stable to the reaction conditions), and it is conceivable that **5** ionized with simultaneous anti migration to give intermediate **16**. However, the existence of intermediate **15** will be demonstrated later under different reaction conditions. An analogous set of reactions was not performed on the corresponding acetoxy bromide, as it was not available in a pure state.

We can now interpret our initial observations from the silver-assisted acetolyses of dibromide **1** and dichloride **2** (Scheme III). These compounds ionize to give a mixture of ions **17** and **18**, which are identical with the ones formed in the electrophilic addition reactions.[1] These first-formed cations are trapped to give the intermediate acetoxy halides in a ratio identical with that of addition.[1] These intermediate compounds then react with a second equivalent of silver acetate to give either 5a,12-diacetoxyhemiisojanusene (**3**) or 6,12-diacetoxy-*cis*-isojanusenes **4** and **13**.

Acid-Catalyzed Rearrangements.—Treatment of 5a,-12-diacetoxyhemiisojanusene (**3**) with perchloric–acetic

SCHEME III

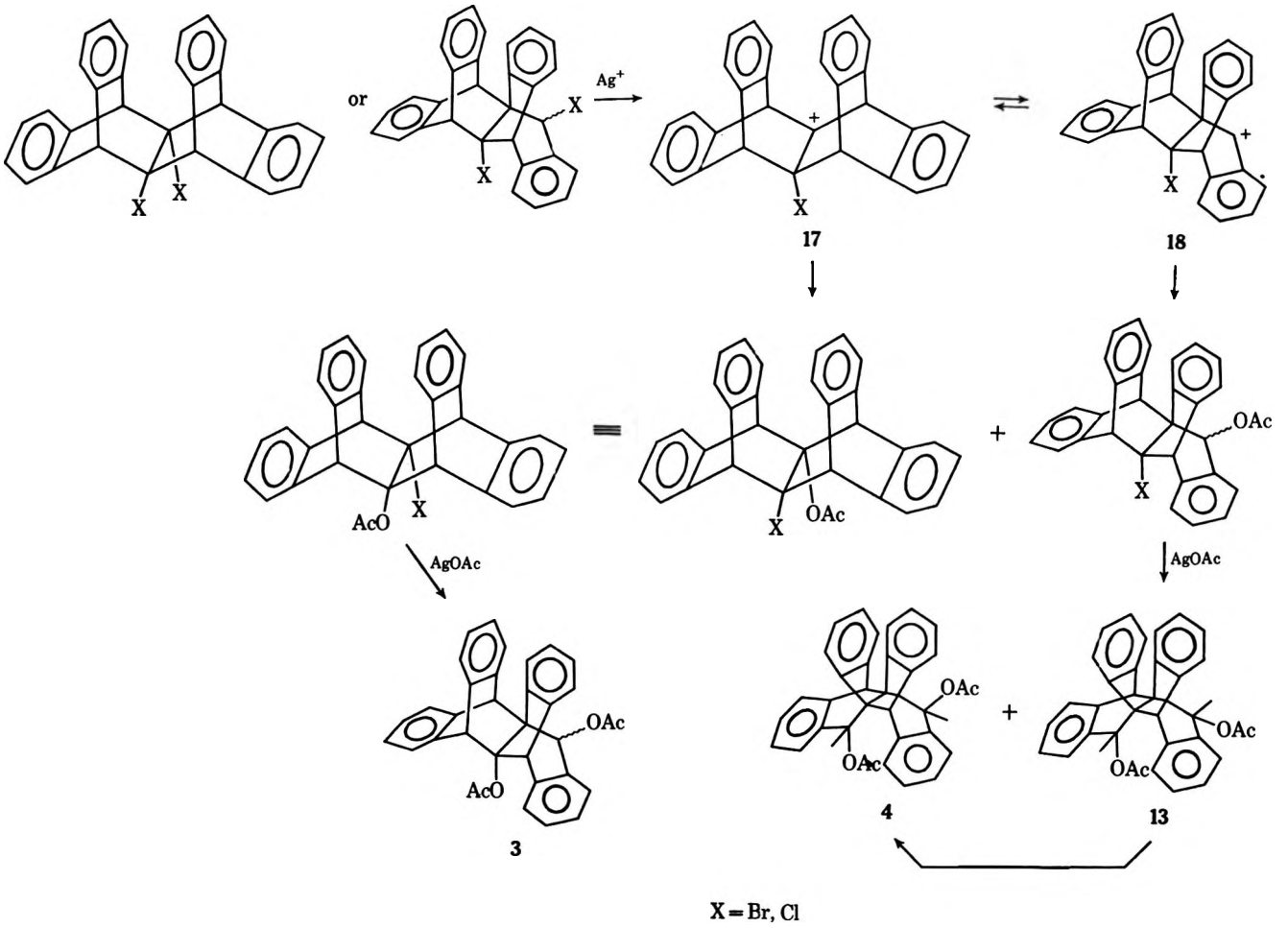


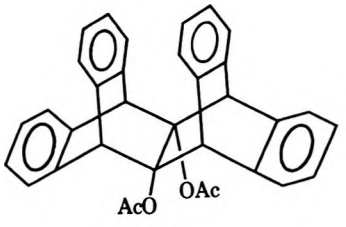
TABLE I

ACID-CATALYZED REARRANGEMENT OF 5a,12-DIACETOXYHEMIISOJANUSENE (3)[a]

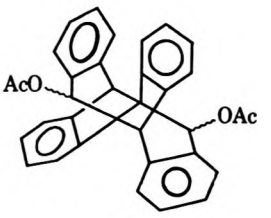
3, mmol	[HClO4], M	H+, mmol	Temp, °C	Time, hr	% recn	% 19	% 20	% 8	8, mmol
0.10	10^{-3}	0.010	90	2.5	100	80	14	6	0.006
0.09	10^{-3}	0.014	95	19	100	77	16	7	0.006
0.10	10^{-3}	0.017	95	144	100	57	29	14	0.014
0.09	10^{-3}	0.080	90	23	100	5	27	68	0.061
0.13	10^{-2}	0.12	25	33	50	78	22		
0.2	10^{-2}	0.12	75	0.25	100	80	20		
0.37	10^{-2}	0.10	105	0.25	100	51	23	26	0.096
0.1	10^{-2}	0.12	80	4.0	100		33	66	0.07

[a] Product analysis was by pmr.

acid solutions under various reaction conditions gave mixtures of 5a,11a-diacetoxyjanusene (**19**), 6,12-di-



19



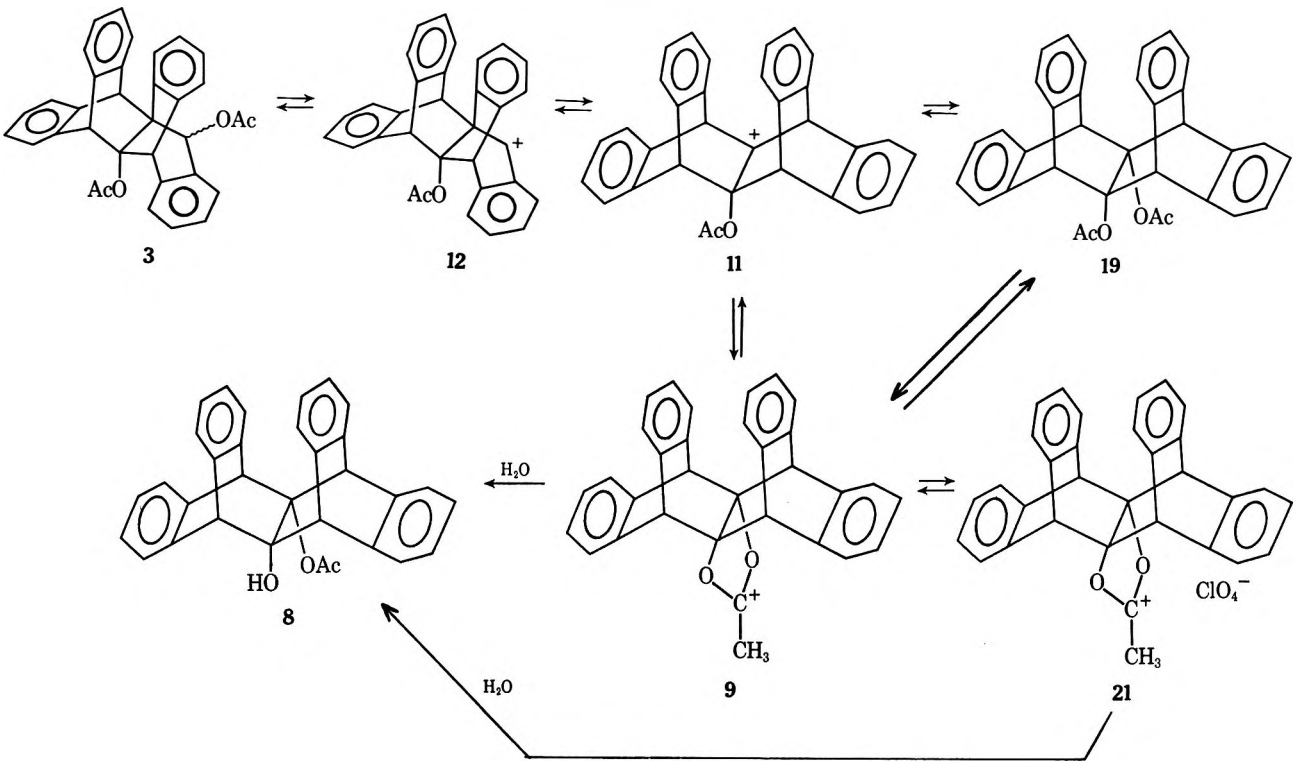
20

acetoxy-*trans*-isojanusene (**20**), and 5a-hydroxy-11a-acetoxyjanusene (**8**) of varying composition. The results are summarized in Table I.

Some immediate observations can be made from the data in Table I. The amount of hydroxyacetate **8** produced in these reactions never exceeded the initial amount of perchloric acid, regardless of the reaction conditions. The amount of **8** also appeared to depend upon reaction time and temperature. Under conditions in which 50% rearrangement occurred, no hydroxyacetate **8** was formed, although the amount of perchloric acid present was equal to the millimoles of starting diacetate **3**. The data also indicated that hydroxyacetate **8** was formed at the expense of diacetate **19**. Finally, when the amount of perchloric acid was about equal to the starting material, diacetate **3**, more diacetate **20** was formed than in examples of less acid, although the initial concentration of acid was the same in both cases.

A mechanistic pathway for the rearrangement of **3** to **19** is described in Scheme IV. Analogous to the solvolysis of 5a-chloro-11a-acetoxyjanusene (**5**), ionization of diacetate **3** gives a mixture of ions **11** and **12**. Cation **11** is trapped rapidly as diacetate **19** or more

SCHEME IV



slowly as acetoxonium ion **9**. This latter ion may then react with acetic acid under acidic conditions to give diacetate **19**,[8] or it can pair with perchlorate ion to form **21**. It is the formation of this salt which explains many of the observations from the data in Table I. Upon aqueous work-up, this salt gives hydroxyacetate **8**,[5] and therefore the amount of **8** cannot exceed the amount of perchloric acid. This salt also serves to tie up perchloric acid so that the effective acid concentration becomes substantially less than the initial concentration. Because of this, the amount of diacetate **20** formed also depends upon the amount rather than the concentration of perchloric acid. In other words, the rearrangement of **19** to **20** appears to stop prematurely, because the effective concentration of perchloric acid is reduced severely.

To this point the discussion has been concerned with the rearrangement of 5a,12-diacetoxyhemiisojanusene (**3**) to the janusene derivatives. The rearrangement of diacetate **3** in the other direction to give an epimeric mixture of 6,12-diacetoxy-*trans*-isojanusenes (**20**) was also examined. This latter reaction was demonstrated to proceed first through *exo*-6,*endo*-12-diacetoxy-*cis*-isojanusene (**4**).

Since diacetate **4** was a kinetic product from the silver-assisted solvolysis of acetoxy chloride **5**, one would expect that this diacetate should be first formed from the ionization of the acetoxy group at C-5a in **3**. When diacetate **4** was treated with perchloric–acetic acid, it rearranged quickly to the *trans*-isojanusene isomer **20**. However, closer examination of this rearrangement by pmr indicated that *endo*-6,*endo*-12-diacetoxy-*cis*-isojanusene (**14**) was formed as an intermediate.

Diacetate **4** was heated at 65° in 0.4 ml of 0.0025 *M* $HClO_4$–HOAc in a sealed nmr tube. From the data in Table II, the half-life for the disappearance of diacetate **4** was calculated to be about 20 min, and the half-life for the disappearance of **14** was about 325 min. Diacetate **4** rearranged to its epimer **14** and to the *trans*-isojanusene compounds **20** at about the same rate. Then diacetate **14** rearranged more slowly to diacetate **20**. The isomeric mixture of **20** consisted of three epimers as detected by pmr and thin layer chromatography (85% was believed to be the "diendo" compound), and their relative ratios remained constant over the reaction time (Scheme V).

TABLE II

ACID-CATALYZED REARRANGEMENT OF *exo*-6,*endo*-12-DIACETOXY-*cis*-ISOJANUSENE (**4**) AT 65°[a]

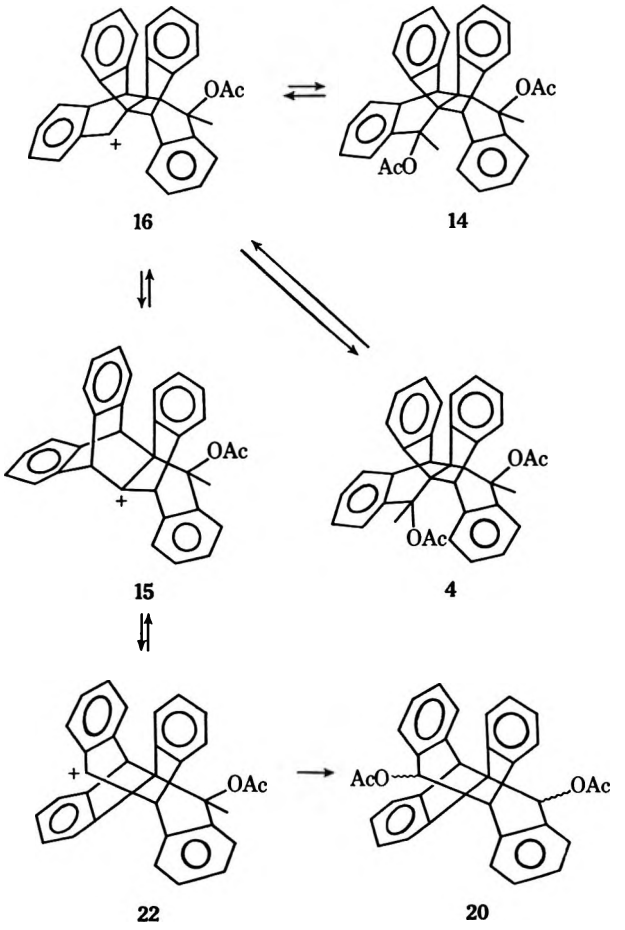
Time, min	% 4	% 14	% 20
5	100	Trace	Trace
20	57	20	23
35	26	37	37
55	20	40	40
80	Trace	50	50
120		50	50
195		43	57
315		33	67
815		11	88
1115		Trace	95
2275			100
5075			100

[a] Product analysis by pmr.

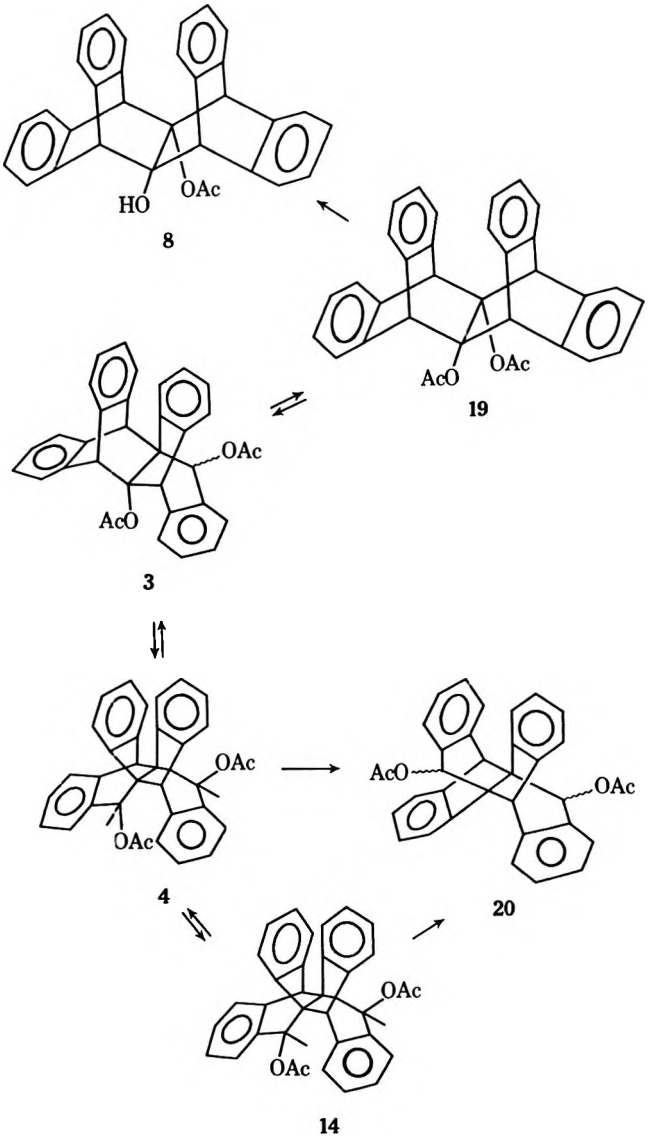
Because diacetate **4** rearranged much faster than diacetate **14**, one can conclude tentatively that the exo substituent ionized faster than the endo one. This is consistent with the preference for exo attack in the *cis*-isojanusene system as described previously. Also, the ground state energy is higher for **4** than for **14**, and therefore the former should be more reactive. Although the presence of ion **15** was uncertain in the silver-assisted solvolysis of acetoxy chloride **5**, its ex-

(8) S. Winstein and R. E. Buckles, *J. Amer. Chem. Soc.*, **65**, 613 (1943).

SCHEME V

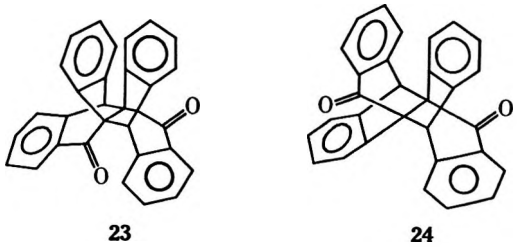


SCHEME VI



istence is necessary to explain the rearrangement of **4** to **20**.

The carbon skeletons of **4** and **20** were shown to be different when they were individually converted to different diketones **23** and **24**. One of the ketones was shown by X-ray crystallography to be a meso compound,[9] and thus had structure **24** (**23** is chiral); since



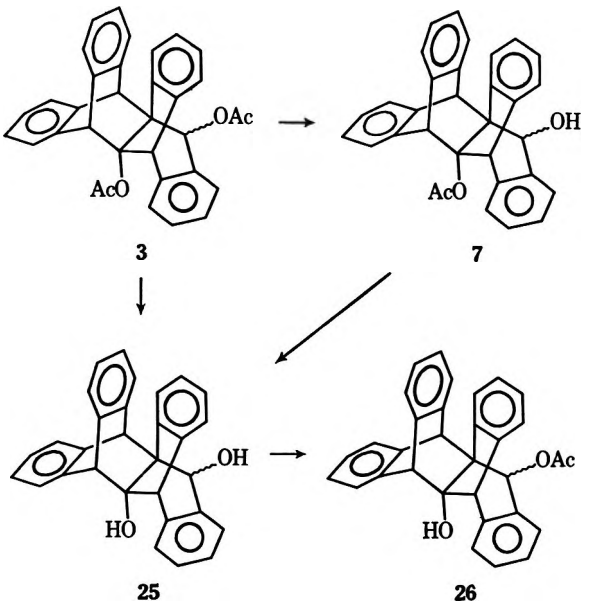
the achiral ketone was formed from the thermodynamically stable diacetate, diacetate **20** was assigned the *trans*-isojanusene structure. Diacetates **14** and **4** were shown to be epimers, because both gave the same diketone **23**.

The rearrangement of 5a,12-diacetoxyhemiisojanusene (**3**) is summarized in Scheme VI. Diacetate **3** rearranges to 5a,11a-diacetoxyjanusene (**19**) and *exo*-6,-*endo*-12-diacetoxy-*cis*-isojanusene (**4**) at a relative rate of 3:1, respectively. Diacetate **4** then quickly epimerizes to the endo,endo diacetate **14** or rearranges to 6,12-diacetoxy-*trans*-isojanusene (**20**). At a slightly slower rate diacetate **14** also rearranges to **20**. At the other end, diacetate **19** slowly rearranges back through diacetate **3** to the isojanusene systems and also is trapped as perchlorate salt **21**, which reacts with water to give hydroxyacetate **8**.

Preparation of Derivatives.—During the course of this work several of the compounds observed were prepared by other routes along with derivatives of some of these compounds. These reactions also revealed some of the structural features of janusene and its skeletal isomers. Diacetate **3** was converted into the corresponding diol **25** with lithium aluminum hydride or upon refluxing in a sodium hydroxide–ethanol mixture. However, treatment of acetate **3** with sodium methoxide–methanol for a shorter time and cooler temperature gave hydroxyacetate **7** which was identical with the hydroxyacetate formed in the silver-assisted solvolysis of acetoxy chloride **6** in wet acetic acid (Scheme VII). Compound **7** could be converted into diol **25** with longer reaction times. This result reflects the steric environment of the two acetoxy groups. The group at the secondary benzylic position is apparently less hindered than the one at the tertiary position. Treatment of diol **25** with acetic anhydride and pyridine yielded hydroxyacetate **26**, which was identical with

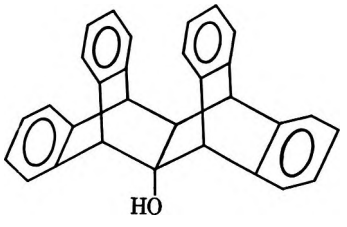
(9) W. M. Macintyre, M. A. Imhoff, and S. J. Cristol, *J. Org. Chem.*, **36**, 1865 (1971).

SCHEME VII

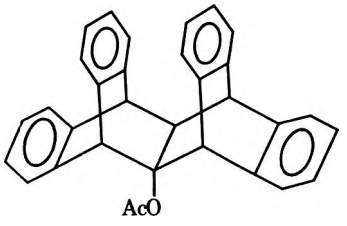


the one formed in the addition of acetic acid to 5a,11a-epoxyjanusene.[1]

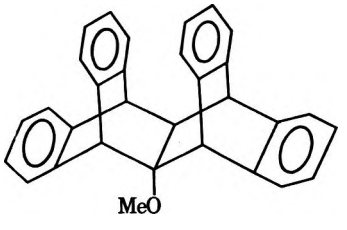
Another indication of the steric hindrance in these systems was observed in an attempt to prepare 5a-hydroxyjanusene (27). Attempted transesterification of



27



28



29

acetate 28 in hydrochloric acid–methanol solution gave mostly starting material 28 and a small amount of 27 and 29. Alcohol 27 was prepared by prolonged treatment of 28 with sodium hydroxide in ethanol.

Finally, hydroxyacetate 8 could be converted into the corresponding diol upon treatment of it with hydroxide in ethanol, or it could be converted into diacetate 19 upon treatment with sulfuric acid and acetic anhydride.

Experimental Section

All nuclear magnetic resonance spectra were taken on a Varian A-60A instrument as saturated solutions in chloroform-d_1 using tetramethylsilane as an internal standard. All chemical shifts are reported in τ units (τ = 10.00 for tetramethylsilane). Infrared spectra were taken on a Beckman IR-5 spectrophotometer in KBr or CCl_4. All elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were uncorrected.

"Work up" involved partitioning the reaction mixture between water and ether, washing the ether layer, drying it over magnesium sulfate, filtering, and evaporating the solvent under reduced pressure.

Reaction of 5a,11a-Dibromojanusene (1) with Silver Acetate in Acetic Acid.—A mixture of 973 mg (1.80 mmol) of 1 and 605 mg (3.61 mmol) of silver acetate was stirred at reflux in 50 ml of acetic acid for 10 hr to yield 764 mg (85%) of crude product. The pmr spectrum of the product mixture showed 85% 5a,12-diacetoxyhemiisojanusene (3) along with 15% *exo*-6,*endo*-12-diacetoxy-*cis*-isojanusene (4). These compounds were obtained pure by fractional crystallization from methanol (compound 4 was less soluble).

Diacetate 3 was recrystallized from methanol: mp 204–207°; pmr ($CDCl_3$) τ 8.87 (s, 3, OAc at C-5a), 7.98 (s, 3, OAc at C-12), 4.99 (s, 2), 4.67 (s, 1), 3.48 (s, 1), 3.0 (m, 16, aromatics).

Anal. Calcd for $C_{24}H_{26}O_4$: C, 81.93; H, 5.22. Found: C, 81.71; H, 5.19.

Diacetate 4 was recrystallized from acetone–95% EtOH: mp 293–296°; pmr ($CDCl_3$) τ 8.80 (s, 3, OAc at C-6), 7.89 (s, 3, OAc at C-12), 5.51 (s, 2), 3.92 (s, 1), 3.63 (s, 1), 2.90 (m, 16, aromatics).

Anal. Calcd for $C_{24}H_{26}O_4$: C, 81.93; H, 5.22. Found: C, 82.06; H, 5.23.

Reaction of 5a,12-Dichlorohemiisojanusene (2) with Silver Acetate in Acetic Acid.—A mixture of 1.20 g (2.63 mmol) of 2 and 670 mg (4.0 mmol) of silver acetate in 60 ml of acetic acid was stirred at reflux for 8 hr. The isolated crude oil, 1.3 g, gave a complicated pmr spectrum. Identified in this spectrum were diacetates 3 and 4 in a ratio of 3:7, respectively. Also present were 5a,11a-dichlorojanusene[1] and a small amount of 5a-chloro-11a-acetoxyjanusene (6).[1]

Reaction of 5a-Chloro-12-acetoxyhemiisojanusene (5) with Perchloric Acid—Acetic Acid Solution.—A solution of 250 mg (0.53 mmol) of a 1:1 mixture of 5a-chloro-11a-acetoxyjanusene (6) and 5a-chloro-12-acetoxyhemiisojanusene (5) in 16 ml of 0.11 *M* perchloric–acetic acid was stirred at room temperature. At 15 min, 1 hr, 2 hr, and 5 hr, a 4-ml aliquot was taken and the product mixture analyzed by its pmr spectrum. The 15-min aliquot showed a mixture of 5 and 6 with the epimeric composition of 5 the same as initially. The other aliquots contained only acetoxy chloride 6.

Reaction of 5a-Chloro-11a-acetoxyjanusene (6) with Sulfuric Acid and Methanol.—A solution of 73 mg (0.15 mmol) of 6 in 1.1 *M* sulfuric acid–methanol was stirred at reflux for 142 hr. The colorless oil, 70 mg, was identified by its pmr spectrum as starting material 6.

Reaction of 5a-Chloro-11a-acetoxyjanusene (6) with Silver Acetate and Acetic Acid.—A mixture of 494 mg (1.04 mmol) of 6 and 174 mg (1.04 mmol) of silver acetate in 35 ml of acetic acid was stirred at reflux for 24 hr. The pmr spectrum of the crude product showed only 5a,12-diacetoxyhemiisojanusene (3). Crystallization from methanol yielded 350 mg (68%) of diacetate 3, mp 204–207°.

Reaction of 5a-Chloro-11a-acetoxyjanusene (6) with Silver Acetate in Wet Acetic Acid.—A mixture of 73 mg (0.15 mmol) of 6, 26 mg (0.15 mmol) of silver acetate, and 26 mg (0.31 mmol) of sodium acetate was dissolved in 10 ml of wet acetic acid (3 ml of water/100 ml of solution). This amounted to 300 mg (16.6 mmol) of water. The mixture was stirred at gentle reflux for 2.5 hr. The pmr spectrum of the product mixture showed that 50% of the starting material remained. Also present were diacetate 3 and hydroxyacetate 7 in a ratio of 3:1, respectively. No 5a-hydroxy-11a-acetoxyjanusene (8)[1] could be detected. Hydroxyacetate 7 was not separated from the reaction mixture, but its properties will be reported later.

Reaction of 5a-Bromo-11a-acetoxyjanusene (10) with Silver Acetate and Acetic Acid.—A mixture of 90 mg (0.17 mmol) of 10 and 33 mg (0.20 mmol) of silver acetate in 12 ml of acetic

acid was stirred for 6 hr at 55°. The crude product, 82 mg (90%), was identified as 5a,12-diacetoxyhemiisojanusene (3).

Reaction of 5a-Bromo-11a-acetoxyjanusene (10) with Silver Acetate in Wet Acetic Acid.—A mixture of 135 mg (0.26 mmol) of 10, 44 mg (0.26 mmol) of silver acetate, and 22 mg (0.27 mmol) of sodium acetate was dissolved in 11.7 ml of wet acetic acid (5 ml of water/100 ml solution). This corresponded to 32.5 mmol of water. The mixture was stirred at 60° for 18 hr. The pmr spectrum of the crude product indicated a 3:2 ratio of diacetate 3 and hydroxyacetate 7, respectively. No 5a-hydroxy-11a-acetoxyjanusene (8)[1] could be detected.

Reaction of 5a-Chloro-12-acetoxyhemiisojanusene (5) with Silver Acetate and Acetic Acid (2 Min).—To a warm solution of 51 mg (0.11 mmol) of 5 in 10 ml of acetic acid was added 18 mg (0.11 mmol) of silver acetate. Two minutes later a white precipitate appeared and the reaction was worked up. The pmr spectrum showed a complex mixture of products which were identified as 25% starting material, 40% *exo*-6,*endo*-12-diacetoxy-*cis*-isojanusene (4), 10% *exo*-6,*exo*-12-diacetoxy-*cis*-isojanusene (13), and 25% of an unknown alcohol. The presence of an alcohol was based upon anomolous peaks in the pmr spectrum of the product mixture and a weak absorption at 3600 cm^{-1} in the infrared spectrum.

Compound 13 could not be separated and characterized: pmr ($CDCl_3$) τ 8.78 (s, 6, OAc), 5.50 (s, 2), 3.89 (s, 2), 2.9 (m, 16, aromatics).

Reaction of 5a-Chloro-12-acetoxyhemiisojanusene (5) with Silver Acetate and Acetic Acid.—A mixture of 64 mg (0.14 mmol) of 5 and 22 mg (0.13 mmol) of silver acetate in 10 ml of acetic acid was stirred at 60° for 45 min. The crude product, 60 mg (85%), was identified by its pmr spectrum as exclusively diacetate 4.

Reaction of 5a,12-Diacetoxyhemiisojanusene (3) in Perchloric Acid–Acetic Acid Solution.—This reaction was performed under a variety of conditions with respect to time, acid concentration, substrate concentration, and temperature. This is one example. A solution of 60 mg (0.12 mmol) of diacetate 3 in 14 ml of 0.001 *M* $HClO_4$–HOAc was stirred at 90° for 19 hr. The crude product mixture (80% yield) was analyzed by its pmr spectrum (Table I). None of the products were separated and characterized but instead were prepared independently and shown to give identical pmr spectra.

Reaction of *exo*-6,*endo*-12-Diacetoxy-*cis*-isojanusene (4) in Perchloric Acid–Acetic Acid Solution.—A solution of 166 mg (0.34 mmol) of diacetate 4 in 11 ml of 0.02 *M* $HClO_4$–HOAc was stirred at 100° for 37 min. The yellow solution was then allowed to cool for 2 hr. The crude product, 141 mg (85%), was identified by its pmr spectrum as an epimeric mixture of 6,12-diacetoxy-*trans*-isojanusene (20). This compound was identical with one of the products from the acid-catalyzed rearrangement of diacetate 3.

One of the epimers of 20 represented about 85% of the mixture and was believed to be the diendo isomer. It was fractionally crystallized from acetone–95% EtOH: mp 267.5–269°; pmr ($CDCl_3$) τ 8.20 (s, 6, OAc), 5.24 (s, 2), 3.85 (s, 2), 2.9 (m, 16, aromatics).

Anal. Calcd for $C_{34}H_{26}O_4$: C, 81.93; H, 5.22. Found: C, 81.71; H, 5.09.

Although the other epimer(s) was not isolated, its pmr spectrum was recorded: pmr ($CDCl_3$) τ 8.27 (s, 3, OAc), 7.72 (s, 3, OAc), 5.44 (s, 1), 5.16 (s, 1), 3.80 (s, 1), 3.60 (s, 1).

Reaction of *exo*-6,*endo*-12-Diacetoxy-*cis*-isojanusene (4) in Perchloric Acid–Acetic Acid Solution (Nmr).—A mixture of 51 mg (0.10 mmol) of diacetate 4 and 9.5 mg of *p*-dinitrobenzene (internal standard) was placed in an nmr tube and partially dissolved in 0.4 ml of 0.0025 *M* $HClO_4$–HOAc. The tube was heated in an oil bath at 65° and removed periodically in order to take a pmr spectrum of the sample. The starting material did not completely dissolve until about 80 min into the reaction.

The intermediate diacetate 14 could not be isolated and characterized. Also attempts to prepare it independently were unsuccessful. Its pmr spectrum was recorded: pmr ($CDCl_3$) τ 8.00 (s, 6, OAc), 5.56 (s, 2), 3.92 (s, 2), 2.9 (m, 16, aromatics).

Preparation of *exo*-6,*endo*-12-Dihydroxy-*cis*-isojanusene.—A solution of 525 mg (1.05 mmol) of diacetate 4 in 50 ml of anhydrous ether was added slowly to a slurry of 435 mg (11.4 mmol) of lithium aluminum hydride in 20 ml of dry ether. The reaction was stirred at room temperature for 17.5 hr and then the excess $LiAlH_4$ destroyed. Work-up was as usual and the product was identified as *exo*-6,*endo*-12-dihydroxy-*cis*-isojanusene by its pmr spectrum. The diol was crystallized from benzene–heptane, yielding 280 mg (68%) of white crystals: mp 260–261.5°; pmr ($CDCl_3$) τ 5.43 (s, 1), 5.34 (s, 1), 5.02 (s, 1), 4.97 (s, 1), 2.9 (m, 16, aromatics).

Anal. Calcd for $C_{30}H_{22}O_2$: C, 86.96; H, 5.31. Found: C, 87.26; H, 5.45.

Preparation of 6,12-Dihydroxy-*trans*-isojanusene.—A solution of 323 mg (0.65 mmol) of diacetate 20 in 30 ml of dry ether was added slowly to a slurry of 270 mg (7.1 mmol) of $LiAlH_4$ in 5 ml of anhydrous ether. The mixture was stirred at room temperature for 22 hr and the excess $LiAlH_4$ was destroyed in the usual manner. The product mixture, 207 mg (77%), was identified by its pmr spectrum as 6,12-dihydroxy-*trans*-isojanusene. The diol was crystallized from CH_2Cl_2–benzene: mp 304–306° dec; pmr ($CDCl_3$) τ 5.50 (s, 2), 5.16 (s, 2), 2.9 (m, 16, aromatics).

Anal. Calcd for $C_{30}H_{22}O_2$: C, 86.96; H, 5.31. Found: C, 83.79; H, 5.37.

Preparation of 5a,12-Dihydroxyhemiisojanusene (25).—A solution of 420 mg (0.84 mmol) of diacetate 3 in 20 ml of anhydrous ether was added slowly to a slurry of 335 mg (8.8 mmol) of $LiAlH_4$ in 10 ml of dry ether. The reaction was stirred at room temperature for 21 hr, after which time the excess $LiAlH_4$ was destroyed. The isolated oil, 306 mg (88%), was identified by its pmr spectrum as 5a,12-dihydroxyhemiisojanusene (25). Recrystallization was from benzene–heptane: mp 248–249°; pmr ($CDCl_3$) τ 7.65 (s, 1, OH at C-5a), 6.8 (m, 1, OH at C-12), 5.87 (s, 1), 5.50 (s, 1), 5.03 (m, 1), 2.9 (m, 16, aromatics).

Anal. Calcd for $C_{30}H_{22}O_2$: C, 86.96; H, 5.31. Found: C, 87.15; H, 5.48.

Preparation of 5a-Acetoxy-12-hydroxyhemiisojanusene (7).—A solution of 328 mg (0.66 mmol) of diacetate 3 in 50 ml of sodium methoxide in methanol (prepared by treating 125 ml of methanol with 0.3 g of sodium) was stirred at 50° for 3.5 hr. The pmr spectrum of the crude product, 300 mg (100%), identified it as hydroxyacetate 7. Crystallization of the hydroxyacetate 7 was from benzene–heptane: mp 228–230°; pmr ($CDCl_3$) τ 8.89 (s, 3, OAc), 7.61 (s, 1, OH), 5.04 (s, 1), 4.92 (s, 1), 4.91 (s, 1), 4.67 (s, 1), 2.9 (m, 16, aromatics).

Anal. Calcd for $C_{32}H_{24}O_3$: C, 84.21; H, 5.26. Found: C, 84.05; H, 5.28.

Preparation of 5a-Hydroxy-12-acetoxyhemiisojanusene (26).—A solution of 149 mg (0.36 mmol) of diol 25 in a mixture of 7 ml of acetic anhydride and 7 ml of pyridine was stirred at 80° for 45 min and then poured into ice. The isolated oil, 166 mg (100%), was identified by its pmr spectrum as 5a-hydroxy-12-acetoxyhemiisojanusene (26). Crystallization of 26 was from methanol: mp 234–235.5°; pmr ($CDCl_3$) τ 8.06 (s, 3, OAc), 5.73 (s, 1), 5.37 (s, 1), 5.02 (s, 1), 3.42 (s, 1), 2.9 (m, 16, aromatics). The spectrum of this compound was identical with the one prepared from the ring opening of 5a,11a-epoxyjanusene in acetic acid.[1]

Anal. Calcd for $C_{32}H_{24}O_3$: C, 84.21; H, 5.26. Found: C, 84.41; H, 5.38.

Preparation of 5a-Hydroxyjanusene (27).—A sodium hydroxide–ethanol solution was prepared by treating 125 ml of 95% EtOH with 0.5 g of sodium. To 75 ml of this solution was added 400 mg (0.91 mmol) of 5a-acetoxyjanusene (28) and the mixture stirred at gentle reflux for 50 hr. The pmr spectrum of the product oil, 313 mg (86%), indicated 5a-hydroxyjanusene as the sole product. Alcohol 27 was crystallized from benzene–heptane: mp 268–270.5°; pmr ($CDCl_3$) τ 8.48 (s, 1, OH), 7.87 (t, 1, J = 2.5 Hz), 5.82 (d, 2, J = 2.5 Hz), 5.72 (s, 2), 2.85–3.40 (m, 16, aromatics).

Anal. Calcd for $C_{30}H_{22}O$: C, 90.45; H, 5.53. Found: C, 90.16; H, 5.39.

Preparation of 5a-Methoxyjanusene (29).—A solution of 203 mg (0.46 mmol) of 5a-acetoxyjanusene (28) in 25 ml of 0.97 *M* H_2SO_4–MeOH was stirred at gentle reflux for 2 days. The crude oil was identified as 5a-methoxyjanusene (29) and was crystallized from benzene–heptane, yielding 142 mg (75%) of white crystals: mp 274–275.5°; pmr ($CDCl_3$) τ 6.80 (s, 3, OMe), 7.70 (t, 1, J = 2.5 Hz), 5.75 (d, 2, J = 2.5 Hz), 5.35 (s, 2), 2.8–3.4 (m, 16, aromatics).

Anal. Calcd for $C_{31}H_{24}O$: C, 90.29; H, 5.83. Found: C, 90.17; H, 5.98.

Reaction of 5a-Acetoxyjanusene (28) with Hydrochloric Acid in Methanol.—A solution of 100 mg (0.23 mmol) of acetate 28 in a mixture of 1 ml of concentrated hydrochloric acid and 15 ml of methanol was stirred at reflux for 8 hr. The reaction mixture was worked up as usual and the pmr spectrum of the

mixture indicated 62% acetate **28**, 19% alcohol **27** (transesterification product), and 19% methyl ether **29** (solvolysis product).

Preparation of 5a,11a-Diacetoxyjanusene (19).—To a solution of 218 mg (0.48 mmol) of 5a-hydroxy-11a-acetoxyjanusene (**8**) in 15 ml of acetic anhydride was added 6 drops of concentrated sulfuric acid. The mixture was stirred at 80° for 15 min and then worked up. The crude product, 265 mg (110%), was identified by its pmr spectrum as 5a,11a-diacetoxyjanusene (**19**). Diacetate **19** was crystallized from methanol: mp 270.5–272°; pmr ($CDCl_3$) τ 8.40 (s, 6, OAc), 4.48 (s, 4), 2.85–3.40 (m, 16, aromatics).

Anal. Calcd for $C_{34}H_{26}O_4$: C, 81.93; H, 5.22. Found: C, 81.77; H, 5.22.

Preparation of 5a,11a-Dihydroxyjanusene.—A solution of 199 mg (0.44 mmol) of hydroxyacetate **8** in 25 ml of sodium methoxide–methanol solution (prepared by treating 100 ml of methanol with 0.25 g of sodium) was stirred at reflux for 2 days. The crude product, 155 mg (85%), was identified by its pmr spectrum as 5a,11a-dihydroxyjanusene and it was crystallized from acetone–95% EtOH: mp >340°; pmr ($CDCl_3$) τ 8.02 (s, 2, OH), 5.57 (s, 4), 2.87–3.27 (m, 16, aromatics).

Anal. Calcd for $C_{30}H_{22}O_2$: C, 86.96; H, 5.31. Found: C, 87.17; H, 5.36.

Registry No.—**3**, 29246-46-6; **4**, 29246-47-7; **7**, 29246-48-8; **19**, 29320-07-8; **20**, 29435-62-9; **25**, 29179-05-3; **26**, 29246-49-9; **27**, 29179-06-4; **29**, 29179-07-5; *exo*-6,*endo*-12-dihydroxy-*cis*-isojanusene, 29179-08-6; 6,12-dihydroxy-*trans*-isojanusene, 29179-09-7; 5a,11a-dihydroxyjanusene, 29246-50-2.

Acknowledgments.—The authors are indebted to the National Science Foundation and to the Institute of General Medical Sciences (Public Health Service Grant GM-12139) for support of this work.

Bridged Polycyclic Compounds. LXVIII. The Proton Magnetic Resonance Spectra of Some Derivatives of Janusene, Hemiisojanusene, and Isojanusene[1]

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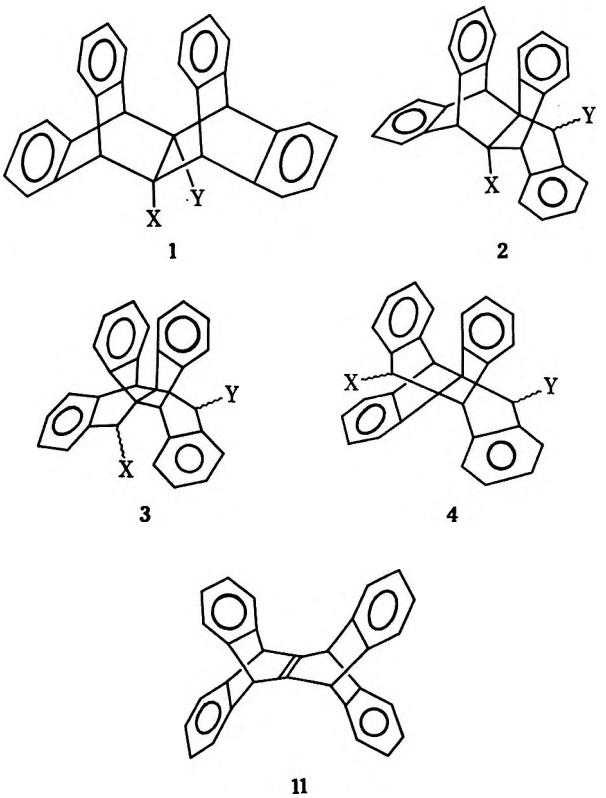
Proton magnetic resonance spectra are given for 41 compounds of various polyhydrodi-*o*-benzenonaphthacene types. Based upon correlations, it is possible to assign structures to many derivatives of janusene, hemiisojanusene, *cis*-isojanusene, and *trans*-isojanusene.

The examination of the carbonium ion reactions of janusene, hemiisojanusene, and isojanusene derivatives[1-4] was made possible by interpretation of pmr spectra. Independent syntheses of most of these compounds was not practicable. However, these spectra, when coupled with certain specific reactions and consideration of possible isomeric structures, appear quite conclusive in making structure assignments.

All spectra were obtained using a Varian A-60A nuclear magnetic resonance instrument. The spectra were taken in deuteriochloroform, usually as saturated solutions, and were scanned over τ 1.7–10.0 using tetramethylsilane (τ 10.00) as an internal standard.

Generally, the pmr spectra of disubstituted janusenes (**1**), hemiisojanusenes (**2**), *cis*-isojanusenes (**3**), and *trans*-isojanusenes (**4**) consist of a complex multiplet centered approximately at τ 3.0, which corresponds to the aromatic hydrogens, and a series of singlets, which arise from the aliphatic hydrogens.[5] Although the general patterns of the singlets are such that skeletal isomers can be easily distinguished, individual proton assignments are difficult and have to be made strictly on the basis of chemical shift data. A number of monosubstituted janusenes (Figure 1), whose structures were derived from chemical knowledge, were prepared as model compounds. In these cases individual proton assignments can be made with certainty, based upon the splitting patterns and expected chemical shifts. The spectral data are listed in Table I.



5a-Bromojanusene (**6**), which was prepared by the addition of hydrogen bromide to dehydrojanusene (**11**),[3] could be converted back to starting olefin upon treatment with potassium *tert*-butoxide. This same monobromide was also prepared from the radical bromination of janusene (**5**).[3] Also, 5a-chlorojanusene (**7**) was prepared by either addition of hydrogen chloride to olefin **11**[3] or as a Diels–Alder adduct from the reaction of

(1) Previous paper: LXVII. S. J. Cristol and M. A. Imhoff, *J. Org. Chem.*, **36**, 1854 (1971).

(2) S. J. Cristol and M. A. Imhoff, *ibid.*, **36**, 1849 (1971). Methods for trivial nomenclature are given in this paper.

(3) S. J. Cristol, M. A. Imhoff, and D. C. Lewis, *ibid.*, **36**, 1722 (1970).

(4) W. M. Macintyre, M. A. Imhoff, and S. J. Cristol, *ibid.*, **36**, 1865 (1971).

(5) The secondary benzylic protons in **2**, **3**, and **4** were split when the substituent was hydroxyl.

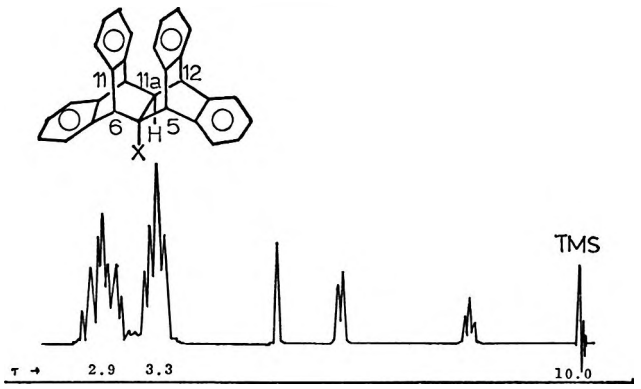


Figure 1.—Structure and general pmr spectrum of a monosubstituted janusene. Omitted from spectrum is absorption, if any, from the substituent.

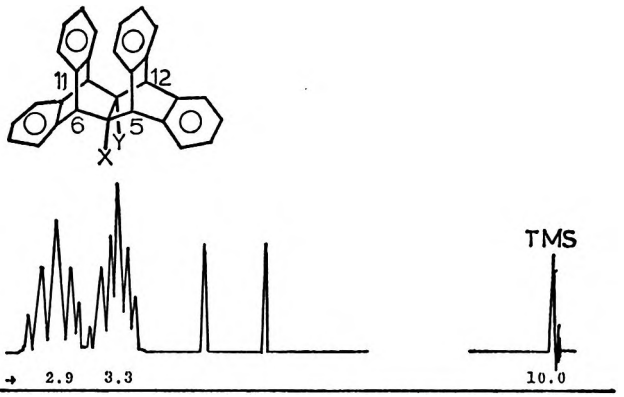


Figure 2.—Structure of a disubstituted janusene when X ≠ Y and a typical pmr spectrum. Omitted from the spectrum are proton absorptions contained in X or Y.

TABLE I

PROTON ASSIGNMENTS IN MONOSUBSTITUTED JANUSENES[a]

		Chemical shifts, τ				
Compd	X	5-H, 6-H	11-H, 12-H	11a-H	Other	J_{H_2},[b]
5	H	5.81	5.81 (2)	7.53 (3)		
6	Br	5.23	5.74 (2)	6.79 (3)		2
7	Cl	5.43	5.77 (2)	7.04 (3)		2
8	OH	5.72	5.82 (2)	7.87 (3)	8.48	2
9	OCH_3	5.35	5.75 (2)	7.70 (3)	6.80	2
10	OAc	4.59	5.74 (2)	7.59 (3)	8.52	2

[a] Values are for centers of resonance patterns and are measured in deuteriochloroform. Integral numbers in parentheses after chemical shift values indicate the complexity of the resonance pattern. [b] Coupling between protons at C-11 and C-12 with C-11a.

anthracene with 7-chlorodibenzobicyclo[2.2.2]octatriene[6] and could be converted to dehydrojanusene (**11**) upon treatment with base. Together, these reactions support the structures indicated in Figure 1 and Table I.

Also shown in Figure 1 is a typical pmr spectrum of a monosubstituted janusene.[6] The singlet absorption is assigned to the protons at C-5 and C-6, the doublet to the hydrogens at C-11 and C-12, and the triplet to the proton at C-11a. Omitted from the spectrum is the singlet absorption when the substituent was either acetate, hydroxyl, or methyl ether.

The data in Table I indicate that the benzhydrylic protons at C-5 and C-6 are deshielded by substituent X in the order OAc > Br > OMe > Cl > OH > H. In these compounds the dihedral angle between the carbon–hydrogen bond and the carbon–substituent bond is about 90°.[7] The relative order of these chemical shifts was used in assigning β hydrogens in disubstituted janusenes and in analyzing various reaction mixtures.

Disubstituted Janusenes.—In the disubstituted janusenes discussed here, the functional groups are located at C-5a and C-11a.[10] As indicated by the structure in Figure 2,[11] there are no adjacent hydrogens, and therefore one would expect only singlets in the aliphatic portion of the spectrum. Also, one may anticipate that the chemical shifts of these absorptions should be similar to those observed for the corresponding singlets in the model compounds. This is, in fact, observed. Figure 2 shows a typical pmr spectrum of a disubstituted janusene, which consists of a complex aromatic proton absorption and a number of singlets depending upon the nature of substituents X and Y. The relative area of the singlets from the bridgehead protons is one-fourth that of the complex multiplet (aromatic protons). When the chemical shifts of the singlets are similar, as in 5a-chloro-11a-methoxyjanusene (**18**), the proton assignments are based upon the relative order of deshielding by the substituents, X and Y, as determined from the model compounds. In other words, a methoxy group deshields the benzhydrylic protons more than a chloro substituent in the model compounds, and, therefore, the downfield singlet in **18** is assigned to the hydrogens at C-11 and C-12. The assignments are listed in Table II.

TABLE II

PROTON ASSIGNMENTS IN THE DISUBSTITUTED JANUSENE SYSTEM

			Chemical shifts, τ		
Compd	X	Y	5-H, 6-H	11-H, 12-H	Other
12	Br	Br	5.13	5.13	
13	Br	OAc	5.13	4.52	8.32
14	Br	OMe	5.17	5.31	6.53
15	Br	Cl	5.15	5.35	
16	Cl	Cl	5.35	5.35	
17	Cl	OAc	5.36	4.49	8.34
18	Cl	OMe	5.38	5.31	6.56
19	Cl	OH	5.33	5.57	7.77
20	OH	OH	5.57	5.57	8.02
21	OH	OMe	5.57	5.34	6.65 (OMe)
22	OH	OAc	5.56	4.53	8.38 (OAc)
23	OAc	OAc	4.48	4.48	8.40
24	Epoxide		5.32	5.32	
11	Dehydrojanusene		4.87	4.87	

Hemiisojanusene.—All of the isolated derivatives of hemiisojanusene were substituted at C-5a and C-12

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

(7) The relative order of deshielding by these substituents is in an order similar to that observed in 7-substituted dibenzobicyclo[2.2.2]octadienes.[8] A different order of deshielding is observed in the chemical shift data of the hydrogens at C-11a where the dihedral angle is about 0°. In these examples the order is Br > Cl > H > OAc > OMe > OH. Here a shielding property from a diamagnetic anisotropic effect presumably masks the deshielding inductive effect of these substituents.[9]

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

(9) J. W. Emsley, J. Feeney, and L. Sutcliffe, "High Resolution Nuclear Magnetic Resonance," Vol. 2, Pergamon Press, Long Island City, N. Y., 1966, p 672.

(10) Other disubstituted janusenes, in which the substituents were located in the aromatic rings, have been reported by S. J. Cristol and D. C. Lewis.[6]

(11) The structure of 5a,11a-dibromojanusene (**12**) was confirmed through X-ray analysis by W. M. Macintyre and A. Tench, private communication.

TABLE III

PROTON ASSIGNMENTS IN THE HEMIISOJANUSENE SYSTEM

Compd	X	Y	Chemical shifts, τ 5-H	6-H	11-H	12-H	Other
25	Cl	Cl	5.58	5.36	5.00	4.34	
26	Cl	OAc	5.57	5.35	4.97	3.48	7.96
27	Cl	OMe	5.64	5.36	5.06	5.27	6.07
28	OH	OH	5.87	5.55	5.03	5.03	7.65, 6.8
29	OH	OMe	5.76	5.41	5.10	5.26	6.26 (OMe), 6.97 (OH)
30	OH	OAc	5.73	5.37	5.02	3.42	8.06 (OAc)
31	OAc	OAc	4.99	4.67	4.99	3.48	7.98, 8.87
32	OAc	OH	4.92	4.67	5.04	4.91	8.89 (OAc), 7.61 (OH)
33	Br	OAc	5.45	5.17	4.96	?[a]	7.97
34	OH	Keto	5.56	4.39	4.59		8.33

[a] Proton absorption was probably buried in the aromatic proton multiplet.

(Figure 3). Inspection of the proposed structures indicated that there are no equivalent protons. Also, none of the aliphatic hydrogens are on adjacent carbons, and therefore only singlets are expected. The observed spectra are consistent with the proposed structures and, in general, consist of a complex multiplet from the aromatic hydrogens, four singlet absorptions (each had a relative area of one-sixteenth that of the complex multiplet), and other singlets if the substituents have hydrogens.

Again, as in the case of disubstituted janusenes, the proton assignments are based upon chemical shifts. Scrutiny of the data in Table III reveals that each spectrum contains an absorption between τ 4.9 and 5.1. This singlet was assigned to the hydrogen at C-11, because it is the one which should be least affected by substituents at C-12 and C-5a. The proton at C-12 is relatively easy to assign due to its characteristic chemical shift which is determined by the deshielding ability of the α substituent. The remaining two singlets are assigned to the hydrogens at C-6 and C-5. Since the environment of the hydrogen at C-6 closely resembled that of the corresponding position in the monosubstituted and disubstituted janusenes, we assign to it the absorption with the more similar chemical shift. This results in the assignment of the lower field singlet to C-6 in all cases. This assignment is further supported when compared to those made for the dibenzobicyclo[3.2.1]octadiene[12] systems. The proton at C-1 in the [2.2.2] system has a lower chemical shift than the hydrogen at C-1 in the corresponding [3.2.1] system. The hydrogen at C-5 in the hemiisojanusene system is viewed as analogous to the one at C-1 in the [3.2.1] system and, therefore, is expected to appear upfield of the hydrogen at C-6.

Added information about the structure of hemiisojanusenes was obtained from the chemical shift data of the substitutents which had hydrogens. This is exemplified by diacetate **31**, which has acetate methyl absorptions at τ 7.98 and 8.87. This latter absorption is higher than normal,[8,12] and examination of Fieser models of diacetate **31** indicates that the substituent at C-5a is positioned in the "shielding cone" of a benzene ring and, therefore, may be expected to be atypically upfield. This assignment was confirmed by comparing hydroxyacetates **30** and **32**.[1,2] In hydroxyacetate **30** the acetoxy substituent at C-5a is replaced by a hydroxyl group, and in the pmr spectrum of **30** only the

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

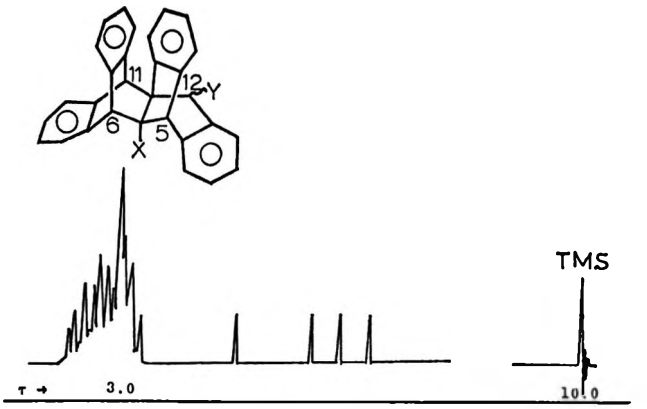
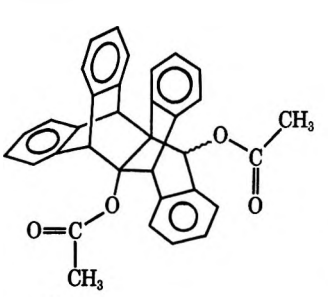


Figure 3.—Structure of a disubstituted hemiisojanusene and a general pmr spectrum. Omitted from the spectrum are the proton absorptions contained in X or Y.

downfield acetate methyl absorption is present. Conversely, the pmr spectrum of hydroxyacetate **32**, in which the acetate at C-12 is substituted by hydroxyl, contains only the upfield acetate methyl absorption.

An alternative structure for hemiisojanusene, which would also contain four unequivalent aliphatic hydrogens, is **35**. In this structure a benzene ring is



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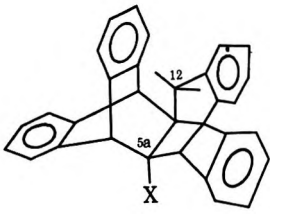

35

located syn to the substituents at C-12. If this were the case, one would expect shielding of the substituents at C-12, but this is not observed. Also, examination of molecular models suggests that the substituents at C-5a should not be greatly shielded. Finally, anti migration, which would give hemiisojanusene **2**, is the preferred direction of rearrangement in similar systems.[13] Thus it seems certain that hemiisojanusene has a structure resembling **2** and not **35**.

(13) (a) S. J. Cristol, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *J. Amer. Chem. Soc.*, **87**, 2879 (1965); (b) S. J. Cristol, F. P. Parungo, and D. E. Plorde, *ibid.*, **87**, 2870 (1965); (c) S. J. Cristol, R. P. Arganbright, and D. D. Tanner, *J. Org. Chem.*, **28**, 1374 (1963).

TABLE IV

PROTON ASSIGNMENTS FOR *cis*-ISOJANUSENE SYSTEM

				Chemical shifts, τ				
Compd	X	C-6[a]	C-12[a]	6-H	12-H	5-H	11-H	Other
36	OAc	exo	endo	3.63	3.92	5.51	5.51	7.89, 8.80
37	OAc	endo	endo	3.92	3.92	5.56	5.56	8.00
38	OH	exo	endo	4.97	5.02	5.34	5.43[b]	
39	OH	endo	endo	5.01	5.01	5.47	5.47	
40	Keto					4.96	4.96	

[a] Configuration of substituent, X; configuration of the proton is opposite. [b] Singlet at τ 5.43 assigned to 11-H since the chemical shift resembles τ 5.47 in the diendo compound **39**.

TABLE V

PROTON ASSIGNMENTS IN DISUBSTITUTED *trans*-ISOJANUSENES

				Chemical shifts, τ				
Compd	X	C-6[a]	C-12[a]	6-H	12-H	5-H	11-H	Other
41	OAc	exo	endo	3.60	3.80	5.44	5.16[b]	7.72, 8.27
42	OAc	endo	endo	3.85	3.85	5.24	5.24	8.20
44	OH	endo	endo	5.16	5.16	5.50	5.50	
45	Keto					4.97	4.97	

[a] Configuration of substituent, X; configuration of the proton is opposite. [b] Singlet assigned to 11-H because the chemical shift resembles τ 5.24 (more closely than τ 5.44) in **42**.

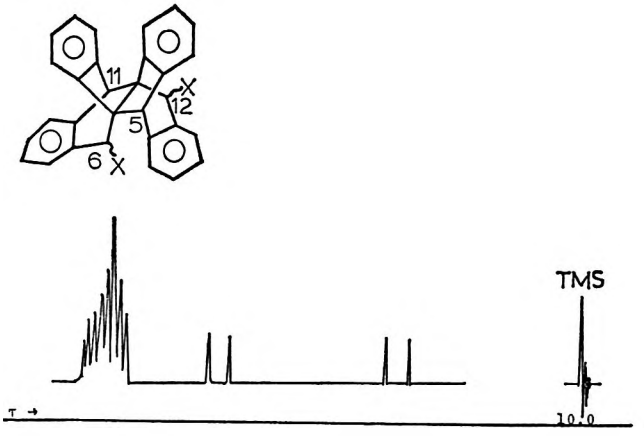

Figure 4.—Structure of a disubstituted *cis*-isojanusene and typical pmr spectrum. Omitted from spectrum are absorptions from protons contained in X.

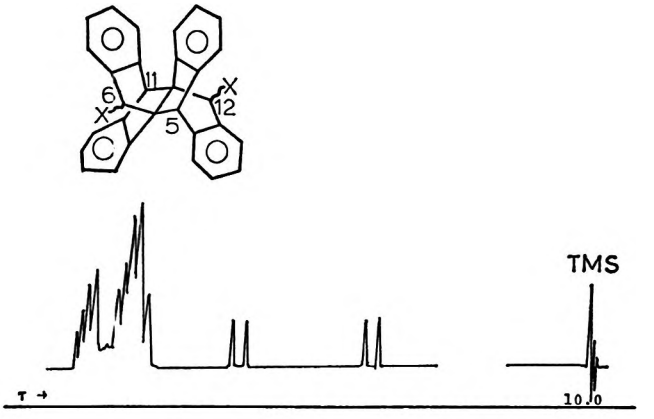

Figure 5.—Structure of *trans*-isojanusene and a typical pmr spectrum. Omitted from spectrum are absorptions from protons contained in X.

Isojanusenes.—Depending upon the configuration of the substituents, the pmr spectra of disubstituted isojanusenes **3** and **4** varies from two to four singlets, not including substituent and aromatic absorptions. *cis*-Isojanusenes and *trans*-isojanusenes have very similar spectra except for the aromatic proton absorptions, and their structures were later differentiated by X-ray crystallography.[4] As indicated from Figures 4 and 5 and Tables IV and V, the pmr spectra show two sets of two aliphatic protons. Two protons have chemical shifts which are characteristic of hydrogens α to a given substituent, and the other two absorb at chemical shifts typical of benzhydrylic protons. The general characteristic of having two groups of two hydrogens is consistent with the proposed structures (Figures 4 and 5).

As in the hemiisojanusene case, diacetate **36** has an acetate methyl absorption at an unusually high chemical shift (τ 8.80) and one at τ 7.89. Examination of Fieser models clearly indicates that exo (quasiaxial) substituents are positioned in the face of a neighboring benzene ring and therefore should be strongly shielded. These same models also indicate that the exo position ought to be sterically hindered. Because the hydrogens at C-6 and C-12 are not equivalent in the pmr spectrum of **36** and because of the observations just noted, diacetate **36** is assigned the exo,endo configuration.

Diacetate **37** is assigned the endo,endo configuration, because both acetate methyl absorptions are at τ 8.00, which indicates that the substituents are endo and equivalent. This structure is preferred to the exo,exo configuration because the chemical shift resembles the endo acetate methyl absorption more than the exo. This compound also was prepared by treatment of **36** under thermodynamic conditions,[2] and molecular models had suggested that the "diendo" compound should be more stable than the "diexo" isomer.

The configuration of the substituents in the *trans*-isojanusene system is known with less certainty than in the *cis*-isojanusenes, because functional groups in *trans*-isojanusenes are not subject to strong shielding effects like those observed in the latter. Diacetate **42** is assigned the "diendo" configuration, since it was prepared under thermodynamic control[2] and Fieser models indicate that the endo,endo epimer should be the most stable. Also, the pmr spectrum shows that the hydrogens at C-6 and C-12, which have the same chemical shift, are equivalent. The exo,endo isomer was detected in the product mixtures in low concentrations. Since the two protons at C-6 and C-12 have different

chemical shifts, we assume that they have different configurations. The chemical shift of the proton at C-12 in **41** was about the same as that in **42**, and therefore we assign it the same configuration. That is to say, the hydrogen is assigned exo and the acetate substituent is designated endo.

Registry No.—**5**, 14707-22-3; **6**, 23646-38-0; **7**, 14596-96-4; **8**, 29179-06-4; **9**, 29179-07-5; **10**, 29309-29-3; **11**, 29309-28-2; **12**, 23646-39-1; **13**, 29308-17-6; **14**, 29309-34-0; **15**, 29428-03-3; **16**, 29309-30-6; **17**, 29309-31-7; **18**, 29308-18-7; **19**, 29308-19-8; **20**, 29246-50-2; **21**, 29308-21-2; **22**, 29308-22-3; **23**, 29428-06-6; **24**, 29308-23-4; **25**, 29309-37-3; **26**, 29308-24-5; **27**, 29308-25-6; **28**, 29428-08-8; **29**, 29308-26-7; **30**, 29246-49-9; **31**, 29246-46-6; **32**, 29246-48-8; **33**, 29308-30-3; **34**, 29308-31-4; **36**, 29246-47-7; **37**, 29308-33-6; **38**, 29179-08-6; **39**, 29308-35-8; **40**, 29339-43-3; **41**, 29309-25-9; **42**, 29309-26-0; **44**, 29309-27-1; **45**, 29595-83-3.

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Bridged Polycyclic Compounds. LXIX. Preparation and Structures of the Diketoisojanusenes[1]

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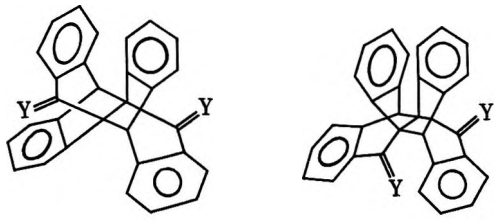
Received August 6, 1970

Oxidation of the 6,12-diols of *trans*- and *cis*-isojanusenes led to the isomeric 6,12-diketojanusenes (**1b** and **2b**). The trans diketone **1b** is achiral and X-ray crystallographic data permit the lower melting isomer to be assigned that structure.

In the course of our work[1,2] on the stereochemistry of the rearrangement reactions of derivatives of janusene (5,5a,6,11,11a,12-hexahydro-5,12:6,11-di-*o*-benzenonaphthacene),[3,4] it became necessary to distinguish *trans*-isojanusene (**1a**) and its derivatives from *cis*-



1 **2**

a, Y = H_2
b, Y = O

isojanusene (**2a**) and its derivatives.[5] To this end we prepared 6,12-diketo-*trans*-isojanusene (**1b**) and 6,12-diketo-*cis*-isojanusene (**2b**) from oxidation of the corresponding alcohols.[2b] Although the pmr spectra and infrared spectra of **1b** and **2b** differed, they could not be used to distinguish between structures **1** and **2**. The lower melting diketone (mp 334–335°) gave a pmr spectrum in chloroform-d_1 with a singlet at τ 4.97 and aromatic proton absorptions at τ 1.94, 2.06, 2.70 and 3.07. The higher melting diketone (mp >360°) gave a pmr spectrum in chloroform-d_1 with a singlet at τ 4.96 and aromatic proton absorptions at τ 2.25, 2.35, 2.72 and 2.99. The infrared spectra were very similar except that the high melting isomer gave strong absorptions at 1248 and 904 cm^{-1} which were absent in the low-melting isomer. The latter, however, gave a medium absorption at 997 cm^{-1} which was not present in the high-melting diketone.

Examination of the structures indicated that **1** should be achiral (meso), while **2** should be chiral. Because of the small amounts of compounds **1b** and **2b** on hand, and the difficulties involved in their preparation, we employed X-ray crystallography in order to distinguish between them rather than the usual chemical resolution techniques. We hoped that simple determination of the space group and of the number of molecules per unit cell might be sufficient to assign unequivocally a meso structure to one of the diketones. Fortunately this hope was realized and it has thus been possible to identify the meso compounds on the basis of simple symmetry arguments.

Neither of the two sets of crystals gave a good diffraction pattern. Only the lower melting ones gave a pattern that was adequate for space group determination, and, in this case, no reflections were observed at a Bragg angle greater than about 40° (Cu Kα radiation). All the crystallographic work was carried out on the lower melting isomer. The crystallographic data obtained follow: system, monoclinic; a = 9.09 Å, b = 8.62 Å, c = 14.74 Å, β = 112° 15′; systematic absences, ($0k0$) with k odd; number of molecules/unit cell, 2 (assuming a crystal density of 1.28 g/cc). These data were consistent with either of the space groups $P2_1$ or $P2_1/m$.

This isomer was then identified as the meso isomer since the *dl* isomer can be excluded from either space group as follows. Let us suppose that the isomer is, in fact, the *dl* isomer; then a unit cell containing two molecules must have one *d* enantiomorph and one *l* enantiomorph. If the cell should have space group $P2_1$, these two enantiomorphs would be related by a twofold screw axis, or the molecule itself would have to contain a twofold screw axis. The former alternative is inadmissible

(1) Previous paper: LXVIII. S. J. Cristol and M. A. Imhoff, *J. Org. Chem.*, **36**, 1861 (1971).

(2) (a) S. J. Cristol and M. A. Imhoff, *ibid.*, **36**, 1849 (1971); (b) S. J. Cristol and M. A. Imhoff, *ibid.*, **36**, 1854 (1971).

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

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

(5) The trivial nomenclature used for these compounds has been described.[2a]

since one diastereoisomer cannot be transformed into the other by the operation of a twofold axis. The second alternative can be excluded since a twofold screw axis cannot be a symmetry element in a nonpolymeric molecule.

If the space group is $P2_1/m$, the symmetry of the cell requires that each of the two molecules in the cell lie on a crystallographic center of symmetry. This requires that the molecules have a center of symmetry, which neither the *d* nor *l* isomer has. Thus the *dl* form cannot crystallize in space group $P2_1/m$.

Since the *dl* isomer cannot be accommodated either in $P2_1$ or $P2_1/m$, with two molecules in the cell, it follows that the isomer with the lower melting point, from crystals of which the diffraction patterns were obtained, must be the meso isomer.

Since the meso isomer itself has a center of symmetry, it is probable that its space group will be $P2_1/m$ with the molecular center of symmetry coinciding with the crystallographic center of symmetry. The space group $P2_1$, however, cannot be entirely ruled out. Fortunately, the above argument does not require an unambiguous space group assignment to the meso form.

Experimental Section

All nuclear magnetic resonance spectra were taken on a Varian A-60A instrument, using saturated solutions in chloroform-d_1 and tetramethylsilane as an internal standard. All chemical shifts are reported in τ units (τ = 10.00 for tetramethylsilane). Infrared spectra were taken on a Beckman IR-5 spectrophotometer in KBr. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points were uncorrected.

Preparation of 6,12-Diketo-*trans*-isojanusene (1b).—To a solution of 78 mg (0.19 mmol) of 6,12-dihydroxy-*trans*-isojanusene[2b] in 20 ml of acetone at 0° was added slowly 1 ml of Jones reagent (6.75 g of CrO_3, 5.75 ml of H_2SO_4, 100 ml of water).[6] The reaction mixture was stirred for 2.5 hr at 0° and then poured into 100 ml of ether. The ether solution was washed with three 200-ml portions of water and once with 150 ml of saturated NaCl solution. The ether solution was dried ($MgSO_4$) and filtered and the solvent evaporated under reduced pressure giving 65 mg (83%) of **1b**. Crystallization was from acetone–95% EtOH: mp 334–335° dec; ν_{max} 1705, 1595, 1463, 1283, 1097, 997, 764, 720, 687 cm^{-1} (KBr); pmr ($CDCl_3$) τ 4.97 (s, 2), 1.90–3.10 (m, 16, aromatics).

Anal. Calcd for $C_{30}H_{18}O_2$: C, 87.80; H, 4.39. Found: C, 87.58; H, 4.39.

Preparation of 6,12-Diketo-*cis*-isojanusene (2b).—To a solution of 330 mg (0.80 mmol) of 6,12-dihydroxy-*cis*-isojanusene[2b] in 20 ml of acetone at 0° was added slowly 4.9 ml of Jones reagent (6.75 g of CrO_3, 5.75 ml of H_2SO_4, 100 ml of H_2O). The reaction mixture was stirred at 0° for 2 hr and then poured into a mixture of 100 ml of methylene chloride and 100 ml of water. The methylene chloride solution was washed twice with 100-ml portions of water, dried ($MgSO_4$), and filtered, and the solvent evaporated under reduced pressure giving 300 mg (91%) of diketone **2b**. Crystallization was from CH_2Cl_2–acetone: mp >360°; ν_{max} 1690, 1590, 1450, 1248, 904, 778, 746, 693 cm^{-1} (KBr); pmr ($CDCl_3$) τ 4.96 (s, 2), 2.25–3.00 (m, 16, aromatics).

Anal. Calcd for $C_{30}H_{18}O_2$: C, 87.80; H, 4.39. Found: C, 87.68; H, 4.34.

Registry No.—**1b**, 29339-42-2; **2b**, 29339-43-3.

Acknowledgment.—The authors are indebted to the National Institute of General Medical Sciences (Public Health Service Grant GM 12139) for support in this work.

(6) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. Weedon, *J. Chem. Soc.*, 39 (1946).

Bridged Polycyclic Compounds. LXX. Rearrangements Accompanying Free-Radical Addition of Thiophenol to 3-Methylenenortricyclene[1]

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The free-radical addition of thiophenol to 3-methylenenortricyclene (1) gives the 1,2-addition product, 3-nortricyclylmethyl phenyl thioether (2), and a variety of unsaturated thioethers (7, 10, 11, and 12) which can be formulated as derivable, under reaction conditions, from the 1,5-homoconjugate addition product, 2-norbornen-2-yl phenyl thioether (3). Variation in product compositions with reagent concentrations demonstrates the existence of classical radical intermediates, rather than a single nonclassical free radical.

A considerable degree of attention has been focussed on homoallyl–cyclopropylcarbinyl rearrangements both in ionic and free-radical systems.[2] Bridged polycyclic compounds have been particularly fruitful in elucidating the nature of homoallyl–cyclopropylcarbinyl free-radical intermediates.[3-21] In continuing our research in this area, we undertook a study of thiophenol addition to the symmetrical olefin, 3-methylenenortricyclene (1).

(1) Paper LXIX: W. M. Macintyre, M. A. Imhoff, and S. J. Cristol, *J. Org. Chem.* **36**, 1865 (1971).

(2) R. Breslow in "Molecular Rearrangements," part I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 289–293, and references therein.

(3) D. I. Davies and S. J. Cristol in "Advances in Free Radical Chemistry," Vol. I, G. Williams, Ed., Logos Press, London, 1966.

(4) C. Walling in "Molecular Rearrangements," part I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 407–451, and references therein.

(5) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *J. Amer. Chem. Soc.*, **80**, 635 (1958).

(6) S. J. Cristol and J. A. Reeder, *J. Org. Chem.*, **26**, 2182 (1961).

(7) S. J. Cristol and D. I. Davies, *ibid.*, **29**, 1282 (1964).

(8) N. O. Brace, *ibid.*, **27**, 3027 (1962).

(9) D. J. Trecker and J. P. Henry, *J. Amer. Chem. Soc.*, **85**, 3204 (1963).

(10) J. W. Wilt and A. A. Levin, *J. Org. Chem.*, **27**, 2319 (1962).

(11) D. I. Davies, J. N. Done, and D. H. Hey, *Chem. Commun.*, **20**, 725 (1966).

(12) C. R. Warner, R. J. Strunk, and H. G. Kuivila, *J. Org. Chem.*, **31**, 3381 (1966).

(13) E. S. Huyser and G. Echegaray, *ibid.*, **27**, 429 (1962).

(14) S. J. Cristol, T. W. Russell, and D. I. Davies, *ibid.*, **30**, 207 (1965).

(15) (a) S. J. Cristol and R. V. Barbour, *J. Amer. Chem. Soc.*, **88**, 4262 (1966); (b) S. J. Cristol and R. V. Barbour, *ibid.*, **90**, 2832 (1968).

(16) S. J. Cristol and R. W. Gleason, *J. Org. Chem.*, **34**, 1762 (1969).

(17) J. A. Berson, C. J. Olson, and J. S. Walia, *J. Amer. Chem. Soc.*, **82**, 5000 (1960).

(18) D. I. Davies, J. A. Claisse, and C. K. Alden, *J. Chem. Soc.*, 1498 (1966).

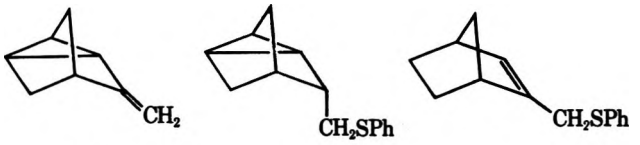
(19) D. I. Davies and C. K. Alden, *ibid.*, 1017 (1967).

(20) J. Warkentin and E. Sanford, *J. Amer. Chem. Soc.*, **90**, 1667 (1968).

(21) S. J. Cristol and A. L. Noreen, *ibid.*, **91**, 3969 (1969).

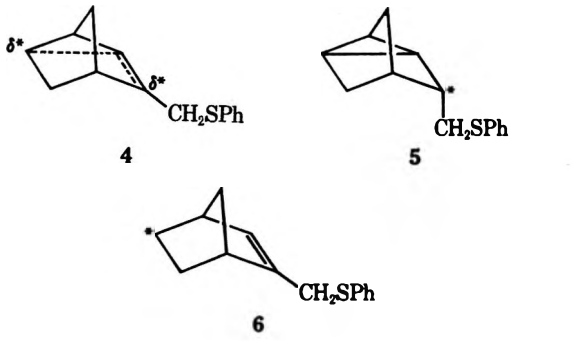
Discussion of Results

Based upon previous work in these laboratories, prediction of both the products and mechanism of thiol addition to **1** seemed straightforward. One would predict the formation of 3-nortricyclylmethyl phenyl



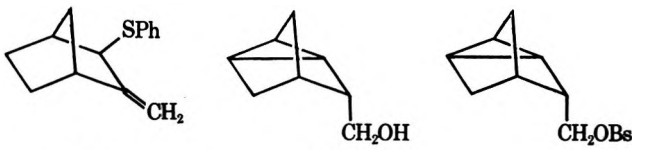
1 **2** **3**

thioether (**2**) *via* 1,2 addition and 2-norbornen-2-yl methyl phenyl thioether (**3**) *via* 1,5-homoconjugate addition. Addition should proceed in an anti-Markovnikov manner with initial phenylthiyl radical attack leading possibly to the delocalized nonclassical radical, **4**, or, more likely,[3,5] to the classical radical **5** which could isomerize to **6**. In either case, chain transfer with the intermediate radicals would lead to the predicted products (**2** and **3**). The distinction between classical and nonclassical intermediates could be made by a study of product distribution with dilution of the reactants.[5]



4 **5** **6**

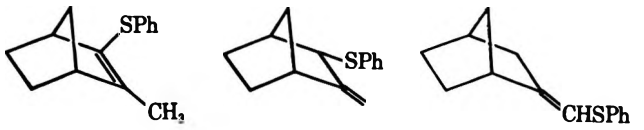
When thiophenol addition to **1**, initiated by ultraviolet irradiation, was actually carried out (at *ca.* 42°) for 30 min, **2** was formed in 80% yield and an unanticipated unsaturated material, *exo*-3-thiophenoxy-2-methylenenorbornane (**7**), was present in 19.5% yield. A third thioether of undetermined structure made up the remaining 0.5% yield of product. Mass spectral analysis showed molecular ions at *m/e* 216



7 **8** **9**

for each of the reaction products, the value expected for a 1:1 adduct. Identification of **2** was established by an independent unequivocal synthesis. Oxidative hydroboration of **1** to give alcohol **8**, conversion to *p*-bromobenzenesulfonate **9**, and direct displacement by thiophenoxide ion to **2** are described in the Experimental Section.

When both **2** and **7** were subjected to the conditions of addition, they were recovered essentially unchanged. However, when the unsaturated thioether **7**, was subjected to prolonged irradiation (*ca.* 2 hr), 2-methyl-3-thiophenoxynorborn-2-ene (**10**) was obtained in 5% yield and a second incompletely characterized product, which appears to be *endo*-3-thiophenoxy-2-methylenenorbornane (**11**), in 7% yield.



10 **11** **12**

When the addition of thiophenol to 3-methylenenortricyclene was carried out over a 150-W incandescent tungsten lamp at 175°, the product mixture contained 34% **2**, 22% **7**, 27% **10**, 14% 8-thiophenoxy-2-methylenenorbornane (**12**), 2% **11**, and 2% of an unknown thioether.

Control experiments, analogous to those previously described and designed to learn the source of **10** and **12**, were carried out. When subjected to severe conditions of thiol addition, **2** and **12** were recovered unchanged in 98 and 100% yield, respectively, while **7** afforded a mixture of 23% **10** and 71% **12**. Under similar conditions, 90% thioether **10** was recovered unchanged with the balance giving 4% **7** and 6% **12**.

The formation of **7**, **10**, and **12** as well as the absence of **3** must be considered and explained. Work by Kharasch and by Oswald and their coworkers has shown that allylic halides and sulfides undergo "allylic reversal" *via* an addition–elimination process with great facility.[22,23] Walling[4] has pointed out, in systems subject to allylic reversal, that isolated products may not be kinetically controlled ones.

For our case, the allylic reversal process fits the available data. The presumed kinetic product **3** suffers attack by phenylthiyl radical at C-3 to give the bis(thioether) radical **13** which subsequently loses phenylthiyl radical from either C-3 or C-8 to give **3** or **7**, respectively. The failure to observe any of the first-formed thioether suggests that equilibration *via* allylic reversal is faster than addition and that equilibration is in favor of the exocyclic thioether **7**.[24]

The appearance of **10** and **12** as major reaction products during thiophenol addition must be the result of reversible allylic hydrogen abstraction. That the rate of hydrogen abstraction competes with those of other free-radical reactions as the temperature is increased is well documented.[4,27] Thus abstraction of the C-8 allylic hydrogen atom from **3** gives radical **14**. Subsequent hydrogen transfer at C-3 affords **12**.

13 **14** **15**

(22) M. S. Kharasch, E. T. Margolis, and F. R. Mayo, *J. Org. Chem.*, **1**, 393 (1936).

(23) D. N. Hall, A. A. Oswald, and K. Griesbaum, *ibid.*, **30**, 3829 (1965).

(24) That the exocyclic olefinic thioether is more stable than its endocyclic isomer is in agreement with the results of studies in similar systems reported in the recent literature.[25,26]

(25) C. K. Alden and D. I. Davies, *J. Chem. Soc. C*, 709 (1968).

(26) (a) P. v. R. Schleyer, Abstracts, 130th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1956, p 290; (b) N. A. Belihova, A. F. Platé, G. M. Tabrina, Kh. E. Sterin, V. M. Lukashina, V. P. Pakhomov, and V. A. Berezkin, *Zh. Org. Khim.*, 498 (1965).

(27) L. H. Gale, *J. Amer. Chem. Soc.*, **88**, 4661 (1966).

TABLE I

ADDITION OF THIOPHENOL TO 3-METHYLENENORTRICYCLENE (1)

Run	Solvent	[Olefin]$_i$, M	Thiol equivalents	Temp, °C	% reaction[b]	% yield of thioethers[c] 2	7	11	10	12	Ratio of tricyclic/olefinic thioethers
1[a]	Neat	4.6	0.96	42	70	80	19.5	0	0	0	4.1
2[a]	$C_6H_3Cl_3$	3.2	0.86	42	64	71	25	2.7	0	0	2.6
3[a]	C_6H_5Cl	1.5	0.99	42	29	59	35	3.1	0	0	1.5
4[d]	Neat	4.8	0.85	175	92	34	22	2.0	27	14	0.54

[a] Reactions were carried out using a GE H100-4A/T 100-W ultraviolet lamp. [b] Per cent reaction was calculated from the amount of converted olefin with respect to the theoretical conversion of olefin. [c] Per cent yields were based on the amount of olefin converted to thioether. In each case the reaction was quantitative. [d] Reactions were carried out using a 150-W unfrosted Westinghouse tungsten lamp, with benzoyl peroxide as initiator.

Likewise hydrogen abstraction from C-3 in **7** gives **15** and hydrogen transfer at C-8 leads to thioether **10**.

Fortunate for the original purpose of this investigation is the fact that there is no crossover between tricyclic and olefinic thioethers under any of the conditions employed. Thus, a comparison of the total of the olefinic thioethers with the amount of tricyclic thioether gives an accurate measure of 1,5-homoconjugate addition *vs.* 1,2 addition, respectively.

To determine the nature of the product-determining radical intermediate(s) involved in the addition of thiophenol, a series of dilution experiments, based on the method used originally by Seubold[28] and used extensively in our laboratory,[5,14,16] was carried out. Dilution of the addition reaction medium causes a decreased rate of chain transfer and hence provides a longer lifetime for the intermediate radicals. If a nonclassical delocalized species (**4**) is the product-determining intermediate, then dilution will effect no change in product distribution. Alternatively, if the product-determining intermediates are the discrete cyclopropylcarbinyl (**5**) and homoallyl (**6**) radicals and if isomerization and hydrogen transfer rates are comparable, significant changes in product distribution toward the olefinic thioether products will be observed. Both chlorobenzene and 1,2,4-trichlorobenzene were used as diluents for the reactants. The results of these experiments are listed in Table I. Although the reactions were not allowed to proceed to completion, the yields were quantitative, based on the per cent of converted olefin. The ratio of tricyclic/olefinic thioether was computed from the yield of **2** and the total yield of unsaturated thioethers. Examination of the experimental results (Table I, runs 1–3) shows that the second possibility obtains. That is, the observed tricyclic/olefinic product ratio decreasing with increasing dilution is incompatible with a single radical intermediate.

Furthermore, comparison of the results of expt. 1 and 4 points up a pronounced temperature effect on the distribution of products. This increase toward the olefinic thioether at elevated temperatures suggests that the energy of activation for cyclopropylcarbinyl–homoallyl radical interconversion, with **4** serving as a transition state, is greater than that for chain transfer.

Thus these experiments, like others that we have reported,[5–7,14–16,21] do not permit the intervention of nonclassical radicals, except as transition states, as important reaction paths. Put another way, the search for π-bridged radicals as product-determining reaction intermediates remains unrewarded.

(28) F. H. Seubold, *J. Amer. Chem. Soc.*, **75**, 2532 (1953).

Nmr and Mass Spectral Studies.—The pmr spectrum of **2** showed no olefinic hydrogen absorptions, indicating that this product was a saturated thioether. A two-proton doublet of doublets (J = 7.2 and 1.5 Hz) at τ 7.28 was assigned to the C-8 methylene protons. A triplet (J = 7.2 Hz), centered at τ 8.26, was attributed to the C-3 methinyl hydrogen. Double irradiation experiments confirmed that the larger coupling constant was a result of the spin–spin interaction between the methinyl and methylene hydrogens. The hydrogen at the C-4 bridgehead position gave a broad unresolved band at τ 8.14. The remaining aliphatic absorptions integrating for eight protons appeared at τ 8.95, 8.76, and 8.64. The aromatic protons displayed a complex multiplet centered at τ 2.80.

The two olefinic hydrogens of the exocyclic unsaturated thioether **7** appeared as a broad band at τ 5.01. This absorption is characteristic of terminal methylene protons and is in particularly good agreement with the chemical shifts of known methylenenorbornane derivatives.[14] Broad apparent "singlets" with chemical shifts at τ 7.68 and 7.28 were assigned to the bridgehead protons at C-4 and C-1, respectively. The endo proton α to the exo thiophenoxy group at C-3 appeared as a poorly resolved doublet (J = 2.0 Hz) at τ 6.36. This small coupling constant is consistent with the long-range splitting commonly observed between the anti C-7 and endo protons of the norbornane system.[29] An exo C-3 proton would be expected to exhibit a coupling constant of *ca.* 3.4–3.8 Hz with the C-4 bridgehead proton.[29] The observed coupling constant of 0 Hz is the expected value for endo C-3 and C-4 bridgehead coupling.

The pmr spectrum of **10** did not show any resonance signals with chemical shifts corresponding to protons α to a thiophenoxy group or to olefinic protons. A broad unresolved band at τ 7.23 was assigned to the two bridgehead protons and a sharp singlet at τ 8.20 integrating for three equivalent hydrogens to the allylic C-8 methyl protons.[30]

The mass spectrum of **10** exhibited a rather intense molecular ion at m/e 216 (35% of base peak). The base peak occurred at m/e 188. The appearance of this fragment was attributed to a retro-Diels–Alder

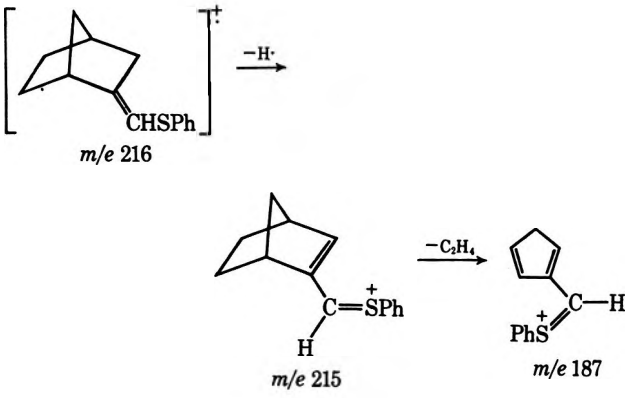
(29) J. C. Davis, Jr., and T. V. Van Auken, *ibid.*, **87**, 3900 (1965).

(30) The C-8 allylic methyl group of the corresponding sulfone gave a singlet at τ 7.77. The magnitude of this downfield shift (*ca.* 0.4 ppm) is similar to that for protons located α to a benzenesulfonyl group. Apparently, the deshielding effect of the sulfone group is transmitted through the double bond. This is analogous with the results reported for the methyl protons of acetaldehyde (τ 7.80) *vs.* the methyl protons of *trans*-crotonaldehyde (τ 7.97).[31]

(31) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Varian Associates, Lithographed by National Press, 1962.

process.[32] This was confirmed by the detection of a metastable ion at m/e 164.

The pmr spectrum of **12** had a signal at τ 4.06 attributable to the single C-8 olefinic proton, which is deshielded by the electronegative thiophenoxy function located at the C-8 position.[33] The exo and endo allylic protons at C-3 gave a complex multiplet at τ 7.95. Broad "singlets" at τ 7.18 and 7.60 were assigned to the bridgehead protons. The normal five-proton aromatic pattern was observed at τ 2.85. The mass spectral fragmentation pattern showed an extremely intense molecular ion as the base peak of the spectrum. The intensity of a molecular ion is dependent on its stability and tendency to fragment.[32] 8-Thiophenoxy-2-methylenenorbornane (**12**) has a conjugated π-electron system. Loss of an electron through electron impact would lead to a stable delocalized molecular



ion. Further, thioethers suffer predominant α- and β-cleavage fragmentations.[34] These pathways are energetically unfavorable in this case because they would require rupture of an sp^2-hybridized σ bond. However, loss of a hydrogen atom from the C-3 position (*i.e.*, β cleavage with respect to the double bond function) affords an allylic cation which finds additional stabilization through resonance involving the unshared electron pairs on the sulfur atom. This allylic cation (m/e 215) can now undergo a retro-Diels–Alder reaction as a secondary fragmentation process to give m/e 187 (77% of base peak). The fragmentation pathway was confirmed by detection of a metastable ion at m/e 163.

Experimental Section

General.—Elemental analyses were determined by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points and boiling points are uncorrected. All solvents and reagents utilized were reagent grade unless specified otherwise.

Spectra.—Pmr data were measured on Varian Associates A-60 and A-60A spectrometers and are reported in τ units, with τ 10.00 for tetramethylsilane as internal standard. Infrared spectra were measured on Perkin-Elmer 21 and Beckman IR-5 spectrophotometers. Mass spectra were taken on a CEC 21-103C mass spectrometer.

Gas Chromatography.—Preparative and analytical gas chromatography were carried out on Varian Aerograph Model A-700 and Model A-90-P3 instruments, respectively, using helium as carrier gas. A 20% fluorosilicon QF-1-0065 (Analabs, Inc.) on Anakrom ABS or Anakrom SD, 70–80 mesh (Analabs, Inc.) column packing was used for both the preparative and analytical gas chromatography. Gas chromatographic analyses were determined on a 7 m × 0.25 in. stainless steel column operated at 185 ± 2° with a carrier gas flow of 130 ml/min. Inert internal standards, 1,2,4-trichlorobenzene (Eastman Organic Chemicals) and 1-bromo-3-chlorobenzene (Matheson Coleman and Bell, Inc.) were used for analytical gas chromatography. The analyses were made by the method of triangulation using an area to weight of compound relationship. Retention times for the thioethers eluted follow: **10**, 31 min; **7**, 39 min; **11**, 41 min; **2**, 53 min, and **12**, 56 min. Preparative gas chromatographic separation and collection were carried out on a 6 m × 0.375-in. copper tubing column at conditions suitable to the separation desired.

Preparation of 3-Methylenenortricyclene (1).—To a solution of Wittig reagent,[35] prepared from 71.0 g (0.199 mol) of methyl triphenylphosphonium bromide and 12.1 g (0.189 mol) of *n*-butyllithium in ether, was added 15.0 g (0.142 mol) of nortricyclanone dissolved in 225 ml of anhydrous ether. The mixture was allowed to stir at room temperature overnight. Cold water was added dropwise until the milky white triphenylphosphine oxide precipitate dissolved. The ethereal solution was separated and the aqueous layer was extracted three times with 200-ml portions of *n*-pentane. The pentane extracts combined with the original ethereal solution were washed three times with 250-ml portions of cold water and with three 100-ml portions of saturated sodium chloride solution. The pentane–ether solution was dried ($MgSO_4$), concentrated, and distilled, bp 45–50° (24 mm), to give 9.5 g (65%) of 3-methylenenortricyclene (**1**) with properties similar to those reported[36] for **1** prepared in a different fashion.

Addition of Thiophenol to 3-Methylenenortricyclene (1). A. Ultraviolet Irradiation.—This entire reaction series was carried out in Pyrex glass tubes (6 mm × 5 cm) which were equipped with rubber serum stoppers. In each case, the tube was placed at a distance of 5 cm from a GE H100-4 A/T 100-W ultraviolet lamp used for free-radical initiation. Each sample was irradiated for a period of 30 min. It was observed that the temperature rose to a maximum of 42° during the irradiation period. Immediately after irradiation, the crude reaction mixture was subjected to gas chromatographic analysis, the results of which are listed in Table I.

First Experiment.—A solution of 151 mg (1.42 mmol) of **1** and 150 mg (1.36 mmol) of thiophenol was irradiated as described above. Immediately after irradiation 62 mg (0.34 mmol) of 1,2,4-trichlorobenzene as internal standard was added to the solution, and gas chromatographic analysis was undertaken.

Second Experiment.—A solution of 79.1 mg (0.746 mmol) of **1**, 70.6 mg (0.642 mmol) of thiophenol, and 106.4 mg (0.588 mmol) of 1,2,4-trichlorobenzene (internal standard) as dilutent was similarly irradiated and analyzed.

Third Experiment.—A solution of 60.9 mg (0.574 mmol) of **1**, 63.0 mg (0.573 mmol) of thiophenol, and 69.8 mg (0.386 mmol) of 1,2,4-trichlorobenzene (internal standard) in chlorobenzene was prepared. This solution, 1.5 *M* in both **1** and thiophenol, was irradiated and analyzed as previously described.

B. Tungsten Lamp Irradiation.—A solution of 35.2 mg (0.332 mmol) of **1**, 31.0 mg (0.282 mmol) of thiophenol, and 1.4 mg (0.006 mmol) of benzoyl peroxide was sealed in a 3 mm × 5 cm Pyrex glass tube. The tube was irradiated at 175 ± 5° over a 150-W tungsten lamp for 2.5 hr. The tube was cooled and opened and the crude reaction mixture was subjected to gas chromatographic analysis. These results are listed in Table I.

This reaction was repeated on a preparative scale and the results obtained were in substantial agreement with those described above. A solution of 3.58 g (33.8 mmol) of **1**, 3.96 g (36. mmol) of thiophenol, 30 mg (0.12 mmol) of benzoyl peroxide, and 2.92 g (16.1 mmol) of 1,2,4-trichlorobenzene as internal standard was sealed in a 1.5 cm × 12 in. thick-walled Pyrex glass tube. The tube was placed over a 150-W tungsten lamp and heated at 170 ± 5° for 2.5 hr. Gas chromatographic analysis indicated yields of 957 mg (16%) of **10**, 2.27 g (38%) of **7**, 1.81 g (30%) of **2**, 643 mg (11%) of **12**, and 353 mg (6%) of two unknown thioethers. These per cent yields are based on an 82% conversion of **1**. The product mixtures from both reactions were combined, separated, and collected by preparative gas chromatography. Separation was effected at a column temperature of 190°. The infrared, pmr, and mass spectra of each com-

(32) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, p 102.

(33) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1959, pp 60–62.

(34) E. J. Levy and W. H. Stahl, *Anal. Chem.*, **33**, 707 (1961).

(35) G. Wittig and A. Schöllkopf, *Chem. Ber.*, **87**, 1318 (1964); *Org. Syn.*, **40**, 66 (1960).

(36) H. Krieger, *Suom. Kemistilehti B*, **37**, 148 (1964).

ponent were taken. Each of the collected materials was placed in an ordinary sublimation apparatus and was allowed to evaporate (with the use of a hot-water bath) and recondense on the cold finger at *ca.* 1-mm pressure. The droplets were drawn up into a (1/8-in. o.d.) glass tube *via* capillary action, sealed, and used for elemental analysis.

Anal. Calcd for $C_{14}H_{16}S$: C, 77.71; H, 7.47. Found for **10**: C, 77.42; H, 7.30. Found for **7**: C, 77.55; H, 7.54. Found for **2**: C, 77.77; H, 7.82. Found for 48% 12–52% **2** mixture: C, 77.77; H, 7.30.

Preparation of 3-Nortricyclomethyl Alcohol (8).—Into a stirred solution of 5.1 g (0.048 mol) of **1** in 40 ml of freshly distilled diglyme was bubbled an excess of diborane gas from a separate reaction flask. The reaction mixture was cooled to 0° and the unreacted diborane gas was destroyed by cautious addition of 20 ml of wet ether and small pieces of ice. When the frothing had stopped, 38 ml of 0.5 *N* sodium hydroxide solution was added; this addition was followed immediately by the careful addition of 19 ml of 30% hydrogen peroxide solution. The reaction mixture was stirred for 30 min and poured into a 150-ml ice–water mixture. The aqueous phase was extracted three times with 100-ml portions of ether. The combined ether extracts were washed ten times with 300-ml portions of cold water and with 100-ml portions of 10% ferrous ammonium sulfate solution until the excess hydrogen peroxide was destroyed. Finally, the ethereal solution was washed with 100-ml portions of saturated brine solution and dried ($MgSO_4$). The ether was removed by distillation through a 12-in. Vigreux column. The oily residues were distilled, bp 105–107° (8 mm), to give a 4.1 g (69%) yield of the desired alcohol (**8**).

Anal. Calcd for $C_8H_{12}O$: C, 77.36; H, 9.76. Found: C, 77.22; H, 9.84.

Preparation of 3-Nortricyclomethyl *p*-Bromobenzenesulfonate (9).—To a solution of 1.18 g (9.6 mmol) of **8** in 6 ml of dry pyridine at −30° was added 2.45 g (9.7 mmol) of *p*-bromobenzenesulfonyl chloride. The mixture was shaken until all of the solids dissolved and was then placed in a freezer at −30° for 15 hr. A yield of 3.19 g (97%) of the desired *p*-bromobenzenesulfonate was obtained. The product was recrystallized from *n*-heptane. A sample, mp 61.5–63.0°, was used for elemental analysis.

Anal. Calcd for $C_{14}H_{15}O_3BrS$: C, 48.99; H, 4.41. Found: C, 48.62; H, 4.46.

Preparation of 3-Nortricyclomethyl Phenyl Thioether (2).—A solution of 5.63 g (16.4 mmol) of **9** in 200 ml of dimethyl sulfoxide was stirred at room temperature. Potassium thiophenoxide (2.43 g, 16.4 mmol) dissolved in 100 ml of dimethyl sulfoxide was added dropwise over a 30-min period. After being stirred for 24 hr the solution was poured into 500 ml of cold water The resulting suspension was extracted three times with 150-ml portions of *n*-pentane. The combined pentane extracts were washed five times with 200-ml portions of cold water and twice with 150-ml portions of saturated sodium chloride solution. The pentane solution was dried ($MgSO_4$) and concentrated by careful distillation through a 12-in. Vigreux column. The oily residues were distilled, bp 135–137° (1.0 mm), to yield 2.38 g (67%) of the desired tricyclic thioether. The gas chromatographic retention time as well as the infrared and pmr spectra were identical with those of **2**, obtained by the free-radical addition of thiophenol to 3-methylenenortricyclene.

Attempted Rearrangement of 3-Nortricyclylmethyl Phenyl Thioether (2).—A solution of 18.9 mg (0.088 mmol) of **2** and 3.6 mg (0.033 mmol) of thiophenol contained in a 3 mm × 5 cm Pyrex glass tube was irradiated with a GE-H100-4A/T 100-W ultraviolet lamp for 1 hr. Immediately after irradiation, the crude reaction mixture was analyzed *via* gas chromatography. This analysis revealed the starting thioether as the only product without any observable rearrangement. Identification was made by retention time comparison with those of thioethers obtained *via* thiophenol addition to 3-methylenenortricyclene.

A solution of 14.6 mg (0.068 mmol) of **2**, 3.0 mg (0.027 mmol) of thiophenol, and 0.5 mg (0.002 mmol) of benzoyl peroxide was sealed in a 1.5 mm × 5 cm Pyrex glass tube. The tube was placed over a 150-W tungsten lamp and irradiated for 2.5 hr at 175 ± 5°. After cooling, the tube was opened and the crude reaction mixture was subjected to gas chromatographic analysis. The results of this analysis indicated a 98% recovery of **2** and 2% an unknown thioether.

Attempted Rearrangement of 8-Thiophenoxy-2-methylenenorbornane (12).—A solution of 10.4 mg (0.048 mmol) of **12** and 1.5 mg (0.014 mmol) of thiophenol was irradiated for 1 hr with a GE-H100-4 A/T 100-W ultraviolet lamp. The temperature was observed to reach 42° maximum throughout the irradiation period. After irradiation, the crude reaction mixture was immediately subjected to gas chromatographic analysis. Again gas chromatographic analysis showed no observable rearrangement, with the starting thioether, **12**, as the sole product.

A solution of 9.8 mg (0.045 mmol) of **12**, 2.2 mg (0.02 mmol) of thiophenol, and *ca.* 0.5 mg (0.002 mmol) of benzoyl peroxide was sealed in a 3 mm × 5 cm Pyrex glass tube. This solution was irradiated over a 150-W incandescent lamp at 175 ± 5° for a 2.5-hr period. The reaction mixture was allowed to cool to room temperature and subjected to gas chromatographic analysis. This analysis showed only **12** with no observable rearrangement.

Rearrangement of *exo*-3-Thiophenoxy-2-methylenenorbornane (7).—A solution of 10 mg (0.046 mmol) of **7** and 2 mg (0.02 mmol) of thiophenol was irradiated for 2 hr with a GE-H100-4A/T 100-W ultraviolet lamp. As before, a 42° temperature maximum was observed during the irradiation period. Gas chromatographic analysis carried out immediately after irradiation indicated the following product distribution: 4.9% **10**, 88% **7**, and 6.9% **11**.

In a sealed 3 mm × 5 cm Pyrex glass tube a solution of 10 mg (0.046 mmol) of **7**, 2.0 mg (0.02 mmol) of thiophenol, and *ca.* 3 mg (0.001 mmol) of benzoyl peroxide was irradiated over a 150-W tungsten lamp for 2 hr at 175 ± 5°. The tube was allowed to cool and the crude reaction mixture was subjected to gas chromatographic analysis, which revealed the following product distribution: 23% **10**, 5.8% **7**, and 71% **12**.

Rearrangement of 2-Methyl-3-thiophenoxynorborn-2-ene (10).—A sealed melting point capillary tube containing a solution of 5.7 mg (0.026 mmol) of **10** and 3.2 mg (0.029 mmol) of thiophenol was irradiated for 2.5 hr with a GE-H 100-4A/T 100-W ultraviolet lamp. Gas chromatographic analysis carried out immediately upon completion of irradiation indicated the complete absence of rearrangement and showed **10** as the sole thioether component.

A solution of 5.5 mg (0.026 mmol) of **10**, 2.0 mg (0.018 mmol) of thiophenol, and *ca.* 0.2 mg (0.001 mmol) of benzoyl peroxide was sealed in a melting point capillary tube. The tube was irradiated over a 150-W tungsten lamp for 2.5 hr at 175 ± 5°. After irradiation, the tube was allowed to cool, opened, and subjected to gas chromatographic analysis, which showed the following product distribution: 90% **10**, 4% **11**, and 5.9% **12**.

Registry No.—**1**, 1974-87-4; **2**, 28253-00-1; **3**, 28253-01-2; **7**, 28256-68-0; **8**, 4337-95-5; **9**, 2752-12-7; **10**, 28253-04-5; **11**, 28253-05-6; **12**, 28253-06-7; thiophenol, 108-98-5.

Acknowledgment.—The authors are indebted to the Institute of General Medical Sciences (Public Health Service Grant GM-12139) for support of this work.

Nuclear Magnetic Resonance and Mass Spectra of Bicyclo[2.2.2]oct-2-ene Derivatives

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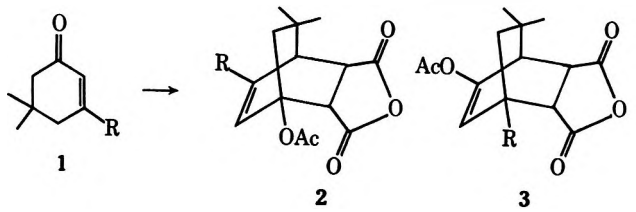
The allylic coupling constants ($J_{2,4}$) in 3-substituted bicyclo[2.2.2]oct-2-enes varies with the nature of the 3 substituent. Substituents capable of electron donation by resonance, as indicated by substituent constant such as σ_R^p, lead to larger coupling constants than those capable of electron withdrawal. The fragmentation of bicyclo[2.2.2]oct-2-ene derivatives on electron impact is dominated by a reverse Diels–Alder reaction with expulsion of an olefin and generation of a cyclohexadienyl radical cation. Enol acetates and bridgehead acetates undergo rearrangement with loss of ketene and transfer of hydrogen. This type of rearrangement occurs more readily than reverse Diels–Alder reactions and directs the fragmentation of members of this particular series.

Our recent observation[2] of the apparent variation of the magnitude of allylic coupling with the 3 substituent in the bicyclo[2.2.2]oct-2-ene system led us to prepare a series of these materials for spectroscopic examination. At this time we would like to discuss the mass spectral fragmentation patterns as well as the allylic coupling exhibited by these substances.

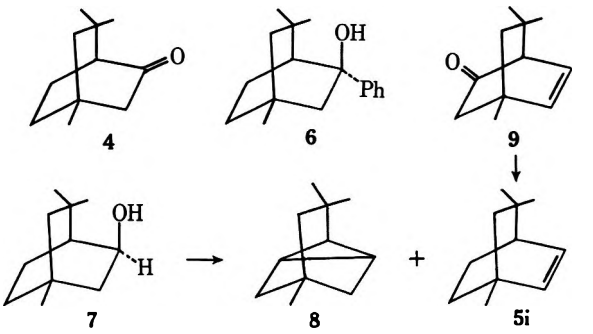
Synthesis.—Having demonstrated[2] the facile conversion of isophorone (**1a**) with maleic anhydride and isopropenyl acetate to the easily separable mixture of adducts **2a** and **3a**, we envisioned preparing a series



a, R = CH_3
b, R = C_6H_5
c, R = *p*-$CH_3OC_6H_4$
d, R = *p*-$NO_2C_6H_4$

of 3-(para-substituted phenyl) derivatives of **2a** *via* analogous reactions. The observation[3] that treatment of acetophenone and acetone with base gave **1b** provided a simple, direct route to the required derivatives of **1**. Reaction of acetophenone and mesityl oxide[4] with sodium hydride in dimethylformamide gave **1b** in 18.5% yield. Similar reaction of *p*-methoxyacetophenone gave **1c** (11%), while *p*-nitroacetophenone gave only a brown intractable solid. Nitration of **1a** gave the desired **1d** in 38% yield. Treatment of ketones **1b** and **1c** with maleic anhydride in isopropenyl acetate gave, in each case, a mixture of adducts separable by crystallization. Similar treatment of **1d** gave only the enol acetate **3d**. The olefinic protons of adducts **2b** and **2c**, as well as those of the corresponding dimethyl esters, appeared as broadened singlets precluding a direct measurement of the coupling constant.

Having earlier prepared ketone **4** from isophorone,[2] we decided to examine some of its tranformation products. Enamine **5a**, enol acetate **5b**, and vinyl chloride **5c** were prepared by standard methods.[5,6] The lithium reagent derived from chloride **5c** gave iodide **5d** and carboxylic acid **5g** when treated with iodine and carbon dioxide, respectively. Reaction of this lithium reagent with acetaldehyde, followed by Jones oxidation, gave unsaturated ketone **5f**. Acid **5g** gave the methyl ester **5h** when treated with diazomethane. Treatment of ketone **4** with phenyllithium gave alcohol **6** which was dehydrated to olefin **5e** with phosphorus oxychloride in pyridine. Interestingly, dehydration of the secondary alcohol **7** (prepared by sodium borohydride reduction of **4**) under similar conditions gave rise to a 9:1 mixture of tricyclic hydrocarbon **8** and the desired olefin **5i**. A pure sample of **5i** was obtained by Wolff–Kishner reduction of ketone **9**.[2]



Allylic Coupling.—The values for the allylic coupling constants ($J_{2,4}$) and the chemical shifts of the olefinic protons of olefins **5a–i** are collected in Table I. It is apparent that increased electron density at the double bond, as evidenced by the chemical shift of the olefinic proton, leads to large coupling constants; electron withdrawal results in smaller coupling. Substituent constants such as σ_R^p and σ_R^m, which emphasize the resonance component of substituent effects, predict this trend; the R value of Swain and Lupton,[7] however, does not correlate this data as well indicating that the field effect cannot be neglected.

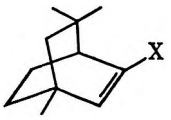
Since these coupling constants are positive,[2,8,9] they should be dominated by σ-bond contributions[10] and can be regarded as occurring through a modified "W" conformation. It is apparent that such coupling, at least when mediated by a double bond, is sensitive to substituent effects.

Mass Spectra.—We have examined the mass spectra of the materials just described as well as others which were available from earlier work in this laboratory.[2] Impetus for this study was provided by the number and

(1) Hercules, Inc., Fellow, 1967–1968.
(2) C. M. Cimarusti and J. Wolinsky, *J. Amer. Chem. Soc.*, **90**, 113 (1968).
(3) J. Wolinsky and H. Hauer, unpublished observation.
(4) A reasonable mechanism for the formation of **1b** from acetone and acetophenone involves Michael addition of acetophenone to mesityl oxide (formed *in situ* from acetone) followed by intramolecular aldol condensation.
(5) W. A. White and H. Weingarten, *J. Org. Chem.*, **32**, 213 (1967).
(6) (a) R. Villotti, H. J. Ringold, and C. Djerassi, *J. Amer. Chem. Soc.*, **82**, 5693 (1960); (b) R. N. McDonald and T. E. Tabor, *ibid.*, **89**, 6573 (1967).
(7) C. G. Swain and E. C. Lupton, Jr., *ibid.*, **90**, 4328 (1968).
(8) R. G. Miller and M. Stiles, *ibid.*, **85**, 1798 (1963).
(9) E. W. Garbisch, Jr., *Chem. Ind. (London)*, 1715 (1964).
(10) M. Barfield, *J. Chem. Phys.*, **41**, 3825 (1964).

TABLE I

NMR SPECTRA OF 3-SUBSTITUTED 1,8,8-TRIMETHYLBICYCLO[2.2.2]OCT-2-ENE DERIVATIVES



No.	X	$J_{2,4}$, Hz[a]	δ, ppm[b]	σ_R^p[c]
a	$(CH_3)_2N-$	1.90	4.74	−0.76[d]
b	AcO−	1.85	5.29	−0.09
c	Cl−	1.75	5.72	−0.24
d	I−	1.63	6.32	−0.11
e	C_6H_5-	*Ca.* 1.4[e]	5.99	−0.09[f]
f	$CH_3\overset{O}{\overset{\|}{C}}-$	1.40	6.73	+0.15
g	HO_2C-	1.30	7.13	
h	CH_3O_2C-	1.30	6.83	+0.11[g]
i	H−		5.93	

[a] All coupling constants were measured at a sweep width of 50 Hz and are the average of several determinations. [b] Measured in CCl_4 except **5g** which was examined in $CDCl_3$ for solubility considerations. [c] Values from L. N. Ferguson, "The Modern Structural Theory of Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1963, p 421. [d] Value for $-NH_2$. [e] Broadening of this signal, although not so extensive as observed for **2b** and **2c**, rendered the measurement very difficult. [f] Value from R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 595. [g] Value for $-CO_2Et$.

variety of functional groups present in these compounds. It was of interest to determine whether such diverse materials could be accommodated by a general fragmentation scheme for bicyclo[2.2.2]oct-2-ene derivatives.

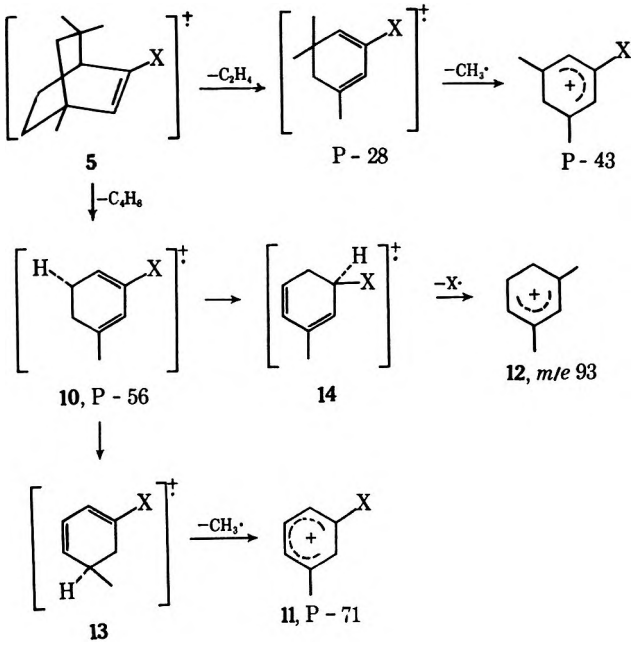
Certain trends are evident from inspection of the principal ions in the spectra of 3-substituted 1,8,8-trimethylbicyclo[2.2.2]oct-2-enes (**5c–i**) collected in Table II. The fragmentation is dominated by a reverse Diels–Alder reaction proceeding from the initially formed radical cation **5** (Scheme I). Loss of isobutylene to give a P − 56 ion, **10**, is prominent in all cases except the enol acetate **5b**. An alternate, but less significant, pathway involves the loss of ethylene to give a P − 28 radical cation which then loses a methyl radical affording a P − 43 cation. This type of fragmentation is documented by appropriate metastable ions in the spectra of compounds **5i**, **5c**, and **5e**.

The remaining important ions can be accounted for by the fragmentation pattern shown in Scheme I. The radical cation **10**, through ejection of a methyl radical or the substituent X, gives rise to cations **11** (P − 71) and **12** (*m/e* 93), respectively. Metastable ions corresponding to one or both of these processes are shown by most of the compounds in this series; for example, vinyl chloride **5c** exhibits metastable peaks at *m/e* 99.8 (**10** → **11**) and *m/e* 67.6 (**10** → **12**). A reasonable pathway for the fragmentation of **10** visualizes 1,5-hydrogen shifts[11] to give radical cations **13** and **14** followed by loss of methyl or X radicals to produce the cyclohexadienyl cations **11** or **12**.

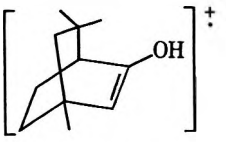
It is apparent that the fragmentation of enol acetate **5b** does not fit Scheme I. The absence of significant ions at P − 56, P − 71, and *m/e* 93 attest to this fact.

(11) *Cf.* J. Wolinsky, B. Chollar, and M. Baird, *J. Amer. Chem. Soc.*, **84**, 2275 (1962), and references cited therein.

SCHEME I



Enol acetate **5b** first loses ketene with transfer of a hydrogen atom to afford radical cation **16**. Further



16

fragmentation of enol **16** then proceeds in a manner analogous to that of the other bicyclooctene derivatives.

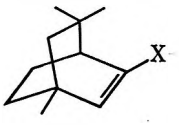
The possibility of transfer of hydrogen *via* a four-membered transition state finds analogy in the rearrangements of benzyl and furfuryl acetates on electron impact.[12] Transfer of hydrogen to carbon *via* a six-membered transition state does not appear to compete favorably, since certain of the major ions produced in the fragmentation of 1,5,5-trimethylbicyclo[2.2.2]-octan-3-one (**4**), *m/e* 151 (34), 112 (41.6), 107 (68.2), 82 (56.2), 81 (52), 69 (64), 67 (89), and 55 (100), are not found to any appreciable extent in the mass spectrum of enol acetate **5b**, and the *m/e* 138 ion of **5b** is not an important ion in the mass spectrum of **4**.

We turn next to a consideration of the principal ions in the mass spectra of enol acetate anhydrides **3a–e** collected in Table III. Inspection of this information supports the conclusion that the enol acetate moiety directs the fragmentation pattern, just as it did for enol acetate **5b**, by transfering a hydrogen atom and losing ketene to give radical cation **17** as shown in Scheme II. Compounds **3a–d** exhibit metastable peaks which document the loss of 42 mass units from the parent ion. Compounds **3a** and **3b** also display metastable peaks for loss of 98 mass units from the parent ion, indicating a competing cleavage of maleic anhydride by a reverse Diels–Alder reaction, or the loss of ketene and isobutylene. A high-resolution study of the *m/e* 242 ion produced from compound **3b** demonstrated that the loss of maleic anhydride occurred with twice the frequency of the loss of ketene and isobutylene.

(12) K. Biemann, "Mass Spectroscopy," McGraw-Hill, New York, N. Y., 1962, p 111.

TABLE II

PRINCIPAL PEAKS IN THE MASS SPECTRA OF 3-SUBSTITUTED 1,8,8-TRIMETHYLBICYCLO[2.2.2]OCT-2-ENES (5b–i)

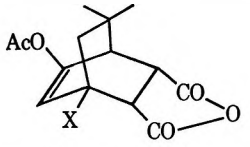


	X =							
Peak	$-OCOCH_3$ (5b)[a]	Cl (5c)	I (5d)	C_6H_5 (5e)	$-COCH_3$ (5f)	CO_2H (5g)	CO_2Me (5h)	H (5i)
Parent	4.7	9.2	14.4	24.6	11.5	3.1	2.4	1.38
P − 28	5.7	12.6	7.2	27.6	2.4	1.9	1.8	2.85
P − 43	1.4	37.2	6.9	96.7	17.4	3.8	3.8	18.8
P − 56	8.8	100.0	62.8	100.0	89.0	100.0	100.0	100.0
P − 71	0.5	13.0	17.6	57.0	65.3	19.7	14.3	62.2
P − X	0.5	4.5	20.0	0.1	17.4	1.1	2.4	0.23
m/e 93	4.6	80.4	100.0	4.0	50.8	98.0	76.0	13.1
m/e 91	8.7	27.2	62.7	26.0	38.6	18.6	36.7	22.5
m/e 79	10.5	7.0	44.3	5.0	12.2	48.3	10.4	12.2
m/e 77	10.8	23.6	41.6	20.8	32.1	53.0	29.0	32.1
m/e 43	4.2	4.0	32.7	11.0	100.0	55.2	23.8	2.4
m/e 41	75.7	18.7	4.9	37.9	32.4	11.3	4.5	20.8
m/e 39	24.3	18.4	32.7	20.6	27.0	44.3	17.7	24.8

[a] Principal ions at *m/e* 166 (20.2%, P − 42), 138 (21.6%, P − 70), 110 (100%, P − 98), 95 (22.2%, P − 113).

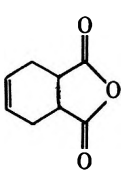
TABLE III

RELATIVE ABUNDANCE OF PRINCIPAL PEAKS IN THE MASS SPECTRA OF 1-SUBSTITUTED 3-ACETOXY-8,8-DIMETHYLBICYCLO[2.2.2]OCT-2-ENE-5,6-DICARBOXYLIC ANHYDRIDES (3a–e)



	X =				
Peak	CH_3 (3a), %	C_6H_5 (3b), %	*p*-MeO-C_6H_4 (3c), %	*p*-NO_2-C_6H_4 (3d), %	AcO– (3e), %
Parent	10.3	12.3	19	4.0	6.1
P − 28	3.3	7.3	4.1	2.4	17.0
P − 42	23.3	22.4	22.0	35.8	13.5
P − 70	24.0	13.5	5.0	9.9	23.0
P − 98	12.7	50.0	75.0	17.6	0.17
P − 140	32.0	28.6	20.0	14.8	68.5
P − 155	69.0	90.9	96.0	42.3	4.0
P − 170	42.8	51.7	39.0	19.0	6.0
m/e 43	100	100	100	100	100

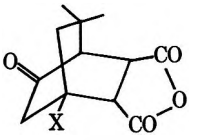
Scheme II suggests a general fragmentation pattern for radical cation **17**. Loss of isobutylene by a reverse Diels–Alder reaction followed by evolution of carbon monoxide and carbon dioxide to give a P − 170 ion **20** finds precedent in the observation that anhydride **21**[13] also loses carbon monoxide and carbon dioxide.



21

Alternatively, maleic anhydride is eliminated generating radical cation **18** which loses a methyl radical to give the P − 155 cation **19**.

The bridgehead acetate **3e** exhibits additional major ions representing loss of 84, 112, 157, 182, 197, and 212 mass units from the parent ion. The P − 84 ion apparently represents the loss of two molecules of ketene with the accompanying transfer of two hydrogen atoms to give radical cation **17** (X = OH). Most of the remaining ions are derived from radical cation **17** by the fragmentation modes already discussed. The P − 112 ion may represent loss of carbon monoxide from the anhydride group of radical cation **17**. The loss of 28 mass units from anhydride **21**[3] and anhydrides **22a** and **22b** have also been observed. The P − 157



22a, X = CH_3
b, X = OAc

ion may arise from ion **19** by loss of a hydrogen molecule.

Finally, the mass spectra of several bicyclo[2.2.2]oct-2-en-5-ones were examined (Table IV). The most abundant ion produced on electron impact of keto olefin **24** (see Scheme III) involves loss of ketene. Loss of ethylene from the parent ion **24** is negligible (less than 0.1%). On the other hand, loss of isobutylene from the radical cation derived from keto olefin **9** to give radical cation **25** competes favorably with loss of ketene forming **26**. Carbon monoxide is ejected from **25**, in a manner which is probably analogous to the loss of carbon monoxide from phenols,[14] to give a *m/e* 80 radical cation, which then loses a hydrogen atom to form a *m/e* 79 cation. The *m/e* 79 cation ejects a hydrogen molecule generating a *m/e* 77 cation.

The bridgehead acetates **27** and **28** lose ketene from the bridgehead acetate group and then exhibit essentially the same fragmentation pattern shown by compounds **24** and **9**. In addition, there is observed a significant loss of acetic acid from the parent radical cation, followed by ejection of a carbon monoxide molecule. This observation suggests that the frag-

(13) S. T. Weininger, V. T. Mai, and E. R. Thornton, *J. Amer. Chem. Soc.*, **86**, 3732 (1964).

(14) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra," Holden-Day, San Francisco, Calif., 1964, pp 20, 21.

SCHEME II

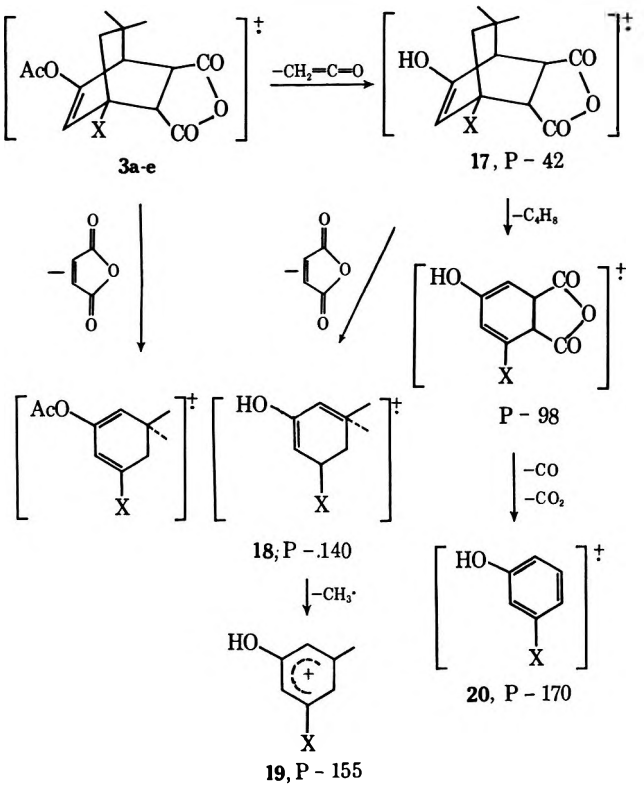
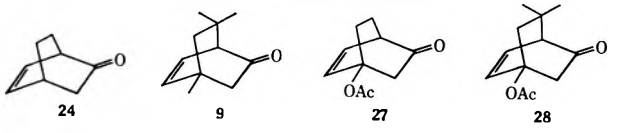


TABLE IV

PRINCIPAL IONS IN THE MASS SPECTRA OF BICYCLO[2.2.2]OCT-2-EN-3-ONES



24 m/e	24 % rel abundance	9 m/e	9 % rel abundance	27 m/e	27 % rel abundance	28 m/e	28 % rel abundance
122	14.6	164	10.2	180	0.8	208	0.7
80	100.0	122	63.2	120	27.4	148	39.1
79	63.3	108	24.4	110	5.4	133	15.8
78	8.2	107	100.0	97	7.2	124	45.1
77	44.6	91	29.7	96	100.0	120	32.4
51	7.8	80	27.1	95	24.2	119	26.8
39	21.0	79	21.7	93	7.0	110	23.9
		77	14.8	92	23	109	74.2
		43	13.0	91	30.8	105	29.2
				77	8.5	91	11.3
				43	72.6	82	10.5
				39	17.5	79	11.3
						77	11.3
						43	100
						41	14.1
						39	17.5

mentation of ketene from the bicylooctenone is at least in part a stepwise process generating radical cation **29** from which acetic acid can be eliminated to give radical cation **30**. Radical cation **30** then fragments as shown in Scheme IV.

In summary, the fragmentation of bicyclo[2.2.2]oct-2-ene derivatives on electron impact is dominated by reverse Diels–Alder reactions with expulsion of olefins such as ketene, maleic anhydride, isobutylene, and ethylene (to a much less significant extent). Loss of radicals from the odd-electron ions which are produced gives relatively stable cyclohexadienyl cations.

Enol acetates and bridgehead acetates have been found to undergo rearrangement with loss of ketene and transfer of hydrogen to oxygen *via* a four-membered transition state. Such rearrangements generally occur more readily than reverse Diels–Alder reactions and tend to direct the fragmentation of derivatives in this series.

Experimental Section[15]

3-Phenyl-5,5-dimethyl-2-cyclohexen-1-one (1b).—The mineral oil was removed from 23.05 g (0.5 mol) of 53.4% sodium hydride dispersion and 200 ml of dimethylformamide (DMF) was added under nitrogen. A solution of 60 g (0.5 mol) of acetophenone in 60 ml of DMF was added over 8 hr and the mixture stirred overnight. A solution of 49 g (0.5 mol) of mesityl oxide in 40 ml of DMF was added and the mixture stirred at 95–100° for 23 hr, cooled, and poured into a mixture of ice and 175 ml of concentrated hydrochloric acid. Ether extraction gave an oil which was distilled *in vacuo* to give 24 g (40%) of recovered acetophenone and a fraction (18.3 g) with bp 121–155° (1 mm). Two crystallizations from pentane gave 11.1 g (18.5%) of **1b**, mp 54–55° (lit.[16] mp 53.8–54.8°).

3-*p*-Methoxyphenyl-5,5-dimethyl-2-cyclohexen-1-one (1c).—A mixture, prepared as described above, from 16.5 g (0.33 mol) of sodium hydride dispersion, 50 g (0.33 mol) of *p*-methoxyacetophenone, 32 g (0.33 mol) of mesityl oxide, and 220 ml of DMF was stirred for 16 hr and processed as above. The resulting oil (72 g) exhibited hydroxyl absorption in the infrared. A 57-g sample was refluxed for 4 hr with 300 mg of *p*-toluenesulfonic acid in 200 ml of benzene and then distilled to give 23 g (46%) of recovered *p*-methoxyacetophenone and 15.6 g, bp 131–168° (0.3 mm). Two crystallizations from 10% ether in pentane gave 7.1 g (11.6%) of **1c**: mp 49.5–50.5°; ir (CCl_4) 6.0 and 6.2 μ; nmr (CCl_4) 1.3 (s, 6), 6.41 (m, 1), and 6.96 and 7.57 ppm (A_2B_2 q, J = 9 Hz, 4).

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.07; H, 8.02.

3-*p*-Nitrophenyl-5,5-dimethyl-2-cyclohexen-1-one (1d).—A 8.7-g (0.0435 mol) sample of **1b** was added over 4 min to 35 ml of concentrated sulfuric acid at −15° under nitrogen. A mixture of 7 ml of sulfuric acid and 8.9 ml of nitric acid was added over 3 min and after a further 10 min the solution was poured into a mixture of ice and ether. The ether was washed with 10% sodium bicarbonate, dried, and evaporated to give an oily solid. Several recrystallizations from hexane–ethyl acetate gave 14.1 g (38.3%) of **1d**: mp 134.5–135°; ir ($CHCl_3$) 5.95 and 6.15 μ; nmr ($CDCl_3$) 1.17 (s, 6), 6.57 (m, 1), and 7.84 and 8.25 ppm (A_2B_2 q, J = 9 Hz, 4).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16. Found: C, 68.63; H, 6.41.

1-Phenyl-3-acetoxy-8,8-dimethylbicyclo[2.2.2]oct-2-ene-5,6-dicarboxylic Anhydride (3b).[17]—A solution of 7.0 g (0.035 mol) of **1b**, 5.0 g of maleic anhydride, and 50 mg of *p*-toluenesulfonic acid in 26 ml of isopropenyl acetate was refluxed for 66 hr, cooled, and diluted with 25 ml of ether. The resulting solid (10.7 g, 90.6%) was fractionally recrystallized from hexane–ethyl acetate. The less soluble fractions were combined and recrystallized several times to give **3b**: mp 176–177°; ir (Nujol) 5.35, 5.55, 5.70, and 6.05 μ; nmr ($CDCl_3$) 1.07, 1.19, and 2.19 (s, 3 each), 1.35 and 1.72 (AB q, J = 14 Hz, 2), 2.80 (m, 1), 3.69 (m, 2), 6.54 (d, J = 2 Hz, 1), 7.55 ppm (m, 5).

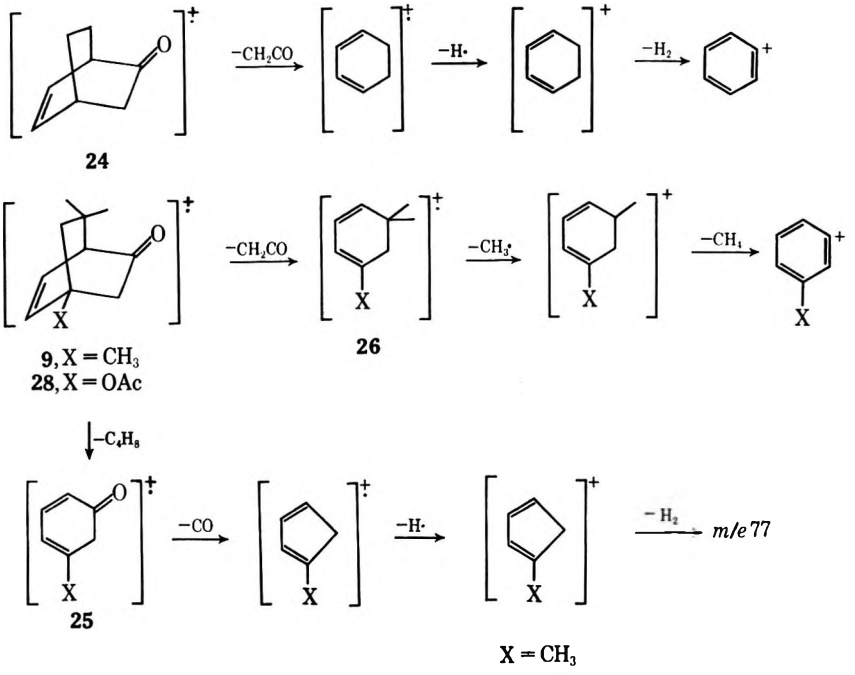
Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.69; H, 6.14.

(15) All boiling points and melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord spectrophotometer, Model 137-B. Nuclear magnetic resonance spectra were determined at 60 Mc on Varian Associates A-60 and A-60A spectrometers. Chemical shifts are recorded in parts per million with reference to tetramethylsilane as internal standard. Mass spectra were recorded on a Hitachi RMU-6A instrument by the Purdue University Spectral Service Department. Microanalyses were performed by Dr. C. S. Yeh and associates. Gas–liquid chromatography was performed mainly on an Aerograph 90-P instrument (column A: 5-ft 20% SE-30 on Chromosorb; column B: 9-ft 30% β,β'-oxydipropionitrile on Chromosorb).

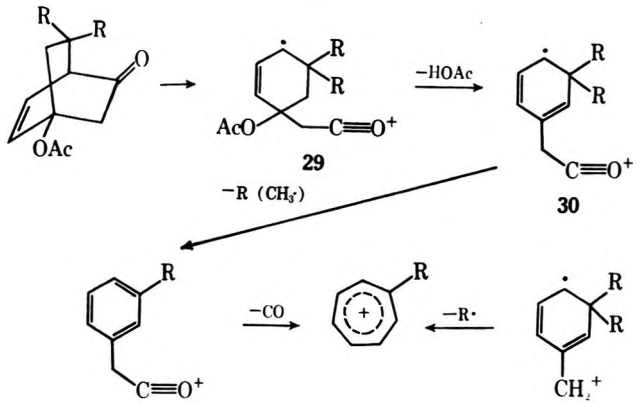
(16) M. Beringer and I. Kuntz, *J. Amer. Chem. Soc.*, **73**, 364 (1951).

(17) The styrene derivatives **2b**, **2c**, and **2d** were distinguished from the isomeric enol acetates **3b** and **3c** by their infrared spectra and by the paramagnetic shift of the C-6 methine caused by the proximity of the C-1 acetoxy group.

SCHEME III



SCHEME IV



1-Acetoxy-3-phenyl-8,8-dimethylbicyclo[2.2.2]oct-2-ene-5,6-dicarboxylic Anhydride (2b).—The more soluble fractions from the reaction of **1b** with maleic anhydride were recrystallized several times to give **2b**: mp 169–169.5°; ir (Nujol) 5.4, 5.6, 5.75, and 6.2 μ; nmr ($CDCl_3$) 0.94, 1.26, and 2.22 (s, 3 each), 1.57 and 2.37 (AB q, J = 12 Hz, 2), 3.33 (m, 1), 3.75 (d of d, $J_{5,6}$ = 9 Hz, $J_{4,5}$ = 3.5 Hz, 1) 4.48 (d, J = 9 Hz, 1), 6.57 (m, 1), and 7.53 ppm (m, 5).

1-(*p*-Methoxyphenyl)-3-acetoxy-8,8-dimethylbicyclo[2.2.2]oct-2-ene-5,6-dicarboxylic Anhydride (3c).—From 6.0 g (0.027 mol) of **1c** was obtained 9.73 g (*ca.* 100%) of crude adduct by treatment with maleic anhydride and isopropenyl acetate. Fractional crystallization from hexane–ethyl acetate gave, as the least soluble component, **3c**: mp 169–169.5°; ir (Nujol) 5.35, 5.6, and 6.05 μ; nmr ($CDCl_3$) 1.03, 1.17, 2.13 (s, 3 each), 6.32 (d, J = 2 Hz, 1), and 6.91 and 7.32 ppm (A_2B_2 q, 4, J = 9 Hz).

Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 67.97; H, 6.13.

1-Acetoxy-3-(*p*-methoxyphenyl)-8,8-dimethylbicyclo[2.2.2]oct-2-ene-5,6-dicarboxylic Anhydride (2c).—The more soluble component from reaction of **1c** proved to be **2c**: mp 161–162.5°; ir (Nujol) 5.35, 5.6, 5.75, and 6.2 μ; nmr ($CDCl_3$) 0.90, 1.20, 2.15 (s, 3 each), 4.28 (d, 1, J = 9 Hz), 6.42 (m, 1), and 6.74 and 7.36 ppm (A_2B_2 q, 4, J = 9 Hz).

Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.09; H, 5.99. Found: C, 68.09; H, 6.21.

1-(*p*-Nitrophenyl)-3-acetoxy-8,8-dimethylbicyclo[2.2.2]oct-2-ene-5,6-dicarboxylic Anhydride.—From 3.2 g (0.013 mol) of **1d** was obtained 2.85 g (63%) of crude adduct. Recrystallization from hexane–ethyl acetate gave only **3d**: mp 198–199°; ir (Nujol) 5.35, 5.5, 5.6, and 6.0 μ; nmr ($CDCl_3$) 1.07, 1.22, and 2.16 (s, 3 each), 6.35 (d, 1, J = 2 Hz), and 7.62 and 8.22 ppm (A_2B_2 q, 4, J = 9 Hz).

Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.49; H, 4.72. Found: C, 62.26; H, 5.05.

3-(*N,N*-Dimethylamino)-1,8,8-trimethylbicyclo[2.2.2]oct-2-ene (5a).—A solution of 0.52 g (0.0055 mol) of titanium tetrachloride in 10 ml of pentane was added to 0.88 g (0.005 mol) of **4** and 1.98 ml (0.03 mol) of dimethylamine in 30 ml of pentane at 0°. After 4 hr the mixture was filtered and the filtrate evaporated *in vacuo* to give an oil. Examination by glc (column A) showed two components in a 1:1 ratio. The first of these was unreacted **4** while the second proved to be the desired enamine. Preparative glc gave a sample of **5a** contaminated by *ca.* 20% of **4**: ir (CCl_4) 6.2 μ; nmr (CCl_4) 0.80 (s, 3), 1.01 and 2.51 (s, 6 each), and 4.28 ppm (d, 1, J = 1.90 Hz).

3-Acetoxy-1,8,8-trimethylbicyclo[2.2.2]oct-2-ene (5b).—A solution of 0.3 ml of **4** in 10 ml of isopropenyl acetate was refluxed with 30 mg of *p*-toluenesulfonic acid for 43 hr and distilled to leave a volume of *ca.* 3 ml. The residue was partitioned between ether and dilute sodium bicarbonate solution. Solvent removal gave an oil which contained one major component in addition to **4** and was purified by preparative glc: ir (film) 5.60, 6.0, and 14.6 μ; nmr (CCl_4) 0.87, 1.03, 1.08, and 2.02 (s, 3 each), and 5.31 ppm (d, 1, J = 1.85 Hz).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.55; H, 9.68.

3-Chloro-1,8,8-trimethylbicyclo[2.2.2]oct-2-ene (5c).—A solution of 1.50 g (0.009 mol) of **4** and 2.2 g (0.011 mol) of phosphorus pentachloride in 20 ml of dichloromethane was refluxed for 22 hr, cooled, and added dropwise to 100 ml of ice–water. The ether extract was washed with saturated sodium carbonate solution. Solvent removal followed by distillation gave 1.14 g (68.5%) of **5c**: bp 45–46° (0.3 mm); ir (film) 6.15 and 13.4 μ; nmr (CCl_4) 0.92, 1.03, and 1.06 (s, 3 each), and 5.72 ppm (d, 1, J = 1.75 Hz). The analytical sample was secured by glc collection.

Anal. Calcd for $C_{11}H_{17}Cl$: C, 71.53; H, 9.27. Found: C, 71.51; H, 9.51.

3-Iodo-1,8,8-trimethylbicyclo[2.2.2]oct-2-ene (5d).—A solution of 1.95 g (0.0105 mol) of chloride **5c** in 10 ml of ether was added to a slurry of 0.75 g (0.107 g-atom) of finely cut lithium wire (high sodium content) in 15 ml of ether. After refluxing for 1 hr, hydrolysis of an aliquot showed only olefin **5i** by glc; *ca.* one-third of this solution was added to a solution of 2.54 g (0.01 mol) of iodine in 10 ml of ether. After 30 min the solution was washed with 100 ml of 5% sodium bisulfite. Solvent removal gave 632 mg (*ca.* 60%) of an oil which showed one peak in addition to solvent on glc (column A). Preparative glc gave a pure sample of

5d: ir (film) 6.28 and 14.1 μ; nmr (CCl_4) 1.00 (s, 6), 1.05 (s, 3), and 6.23 ppm (d, 1, J = 1.63 Hz).

Anal. Calcd for $C_{11}H_{17}I$: C, 47.85; H, 6.20. Found: C, 47.87; H, 6.21.

3-Phenyl-1,8,8-trimethylbicyclo[2.2.2]oct-2-ene (5e).—From the reaction of 1.68 g (0.01 mol) of **4** and phenyllithium (prepared from 18.5 g (0.12 mol) of bromobenzene and 2.1 g (0.3 g-atom) of lithium there was isolated a crude product which was chromatographed over alumina. A total of 0.6 g of alcohol **6** was obtained which was contaminated with unreacted ketone **4**. This material was dissolved in 5 ml of pyridine at 0° and stirred with 0.7 ml of phosphorus oxychloride for 2 hr. This mixture was poured into ether and dilute hydrochloric acid. The ether layer was separated and evaporated to give 430 mg of oil which contained one major component in addition to *ca.* 10% of ketone **4**. Preparative glc gave a pure sample of **5e**: ir (film) 6.24, 6.71, and 6.9 μ; nmr (CCl_4) 0.92, 1.10, and 1.13 (s, 3 each), 5.99 (d, 1, J = 14 Hz), and 7.0–7.5 ppm (m, 5).

Anal. Calcd for $C_{17}H_{22}$: C, 90.20; H, 9.80. Found: C, 90.10; H, 9.98.

3-Acetyl-1,8,8-trimethylbicyclo[2.2.2]oct-2-ene (5f).—A solution of 2.0 ml (large excess) of acetaldehyde in 10 ml of ether was added to a solution of lithium reagent prepared from 910 mg (5 mmol) of chloride **5c** and 0.7 g (0.1 g-atom) of lithium. After 10 min the solution was decanted from excess lithium and poured into water and ether. The ether solution was evaporated to give an oil which was dissolved in 10 ml of acetone and treated with 2 ml of Jones reagent. After processing in the usual manner 780 mg of oil was obtained which contained olefin **5i** and ketone **4** in addition to the desired **5f**. Preparative glc gave a sample of **5f**: ir (CCl_4) 5.95 and 6.2 μ; nmr (CCl_4) 0.64, 1.08, 1.17, and 2.19 (s, 3 each), and 6.73 ppm (d, 1, J = 1.40 Hz). The analytical sample was secured by preparative glc.

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.33; H, 10.18.

1,8,8-Trimethylbicyclo[2.2.2]oct-2-ene-3-carboxylic Acid (5g).—The remaining two-thirds of the solution of lithium reagent prepared above was added to a stirred slurry of *ca.* 30 g of powdered Dry Ice in 25 ml of ether. After 90 min the mixture was poured into 60 ml of water containing two potassium hydroxide pellets. The aqueous layer was separated, acidified carefully, saturated with salt, and extracted with ether. Solvent removal and recrystallization from pentane gave 838 mg (*ca.* 68%) of acid **5g**: mp 135–136°; ir ($CHCl_3$) 2.8–4.0 (broad), 5.92, and 6.15 μ; nmr ($CDCl_3$) 0.77, 1.07, and 1.15 (s, 3 each), and 7.13 ppm (d, 1, J = 1.30 Hz). Sublimation at 80° (0.1 mm) gave the analytical specimen, mp 135.5–136°.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.45; H, 9.20.

The corresponding methyl ester **5h** was prepared from 300 mg (1.54 mmol) of **5g** and excess ethereal diazomethane. Solvent removal gave 312 mg (97%) of an oil which was purified by preparative glc to give pure **5h**: ir (film) 5.80 and 6.15 μ; nmr (CCl_4) 0.73, 1.08, 1.13, and 3.65 (s, 3 each), and 6.83 ppm (d, 1, J = 1.30 Hz).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.00; H, 9.64.

1,8,8-Trimethylbicyclo[2.2.2]oct-2-ene (5i).—A mixture of 0.83 g (0.005 mol) of 9,[2] 5 g of hydrazine hydrate, and 5 g of potassium hydroxide was refluxed for 90 min in 25 ml of diethylene glycol and then distilled until the internal temperature reached 190°. The solution was refluxed for 5 hr, cooled, diluted with water, and extracted with ether. Solvent removal gave 307 mg (36%) of oil which showed one peak on glc. Collection of this material gave pure **5i**: ir (film) 6.2 and 14.2 μ; nmr (CCl_4) 0.80, 1.01, and 1.03 (s, 3 each), 5.77 (d, 1, $J_{2,3}$ = 8.5 Hz), and 6.24 ppm (d of d, 1, $J_{2,3}$ = 8.5, $J_{2,4}$ = 6.5 Hz).

Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 88.16; H, 12.33.

***exo*-1,8,8-Trimethylbicyclo[2.2.2]octan-3-ol (7).**[18]—An amount of 1.55 g (0.009 mol) of **4** was reduced with 0.8 g (0.02 mol) of sodium borohydride in 40 ml of cold methanol. After 2 hr the mixture was partitioned between ether and water to give an oil which crystallized from 10 ml of pentane to give 1.42 g (90.5%) of **7**: mp 55.5–56.5°; ir ($CDCl_3$) 2.7 and 2.9 μ; nmr (CCl_4) 0.80, 0.98, and 1.18 (s, 3 each), and 4.07 ppm (m, 1).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.71; H, 12.13.

1,8,8-Trimethyltricyclo[2.2.2.$0^{3,5}$]octane (8).—A solution of 400 mg (0.00024 mol) of **7** in 4 ml of pyridine was stirred for 3 hr with 0.25 ml of phosphorus oxychloride at ambient temperature and then partitioned between ether and dilute hydrochloric acid. Drying and solvent removal gave 280 mg of oil which showed one peak on glc (column A, 140°). Preparative glc gave a sample of **8** [nmr (CCl_4) 0.88 (s, 3), 1.01 (s, 6), and 0.32–2.15 ppm (m, *ca.* 9)], which also exhibited weak signals in the olefinic region corresponding to those of **5i** (*ca.* 15% by integration). Analytical glc (column B, 85°) indicated that this material contained *ca.* 10% of olefin **5i**. The analytical specimen was secured by preparative glpc: mass spectrum (70 eV) m/e (rel intensity) 150 (24), 135 (32), 107 (40), 95 (27), 94 (100), 93 (88), 91 (24), 81 (24), 80 (40), 79 (72), 77 (24), and 41 (32).

Anal. Calcd for $C_{11}H_{18}$: C, 87.95; H, 12.07. Found: C, 88.13; H, 12.34.

Registry No.—**1c**, 29339-44-4; **1d**, 29339-45-5; **2b**, 29339-46-6; **2c**, 29339-47-7; **3a**, 29339-48-8; **3b**, 29339-49-9; **3c**, 29339-50-2; **3d**, 39339-51-3; **3e**, 29453-56-3; **5a**, 29339-52-4; **5b**, 29339-53-5; **5c**, 29339-54-6; **5d**, 29339-55-7; **5e**, 29339-56-8; **5f**, 29339-57-9; **5g**, 29339-58-0; **5h**, 29339-59-1; **5i**, 29339-60-4; **7**, 29339-61-5; **8**, 29339-62-6; **9**, 17760-98-4; **24**, 2220-40-8; **27**, 17761-01-2; **28**, 17761-00-1.

(18) The *exo*-hydroxyl group is indicated by the paramagnetic shift of 0.10 ppm for one of the *gem*-methyl groups. The reduction of camphor[19] is known to give a predominance (90%) of isoborneol. The *gem*-dimethyl group in **4** should hinder exo attack to a greater degree than in camphor, since it lies closer to the carbonyl groups.

(19) D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.*, **72**, 5743 (1950).

The Stereospecific Intramolecular Insertion of the Cyclopropylidenes Produced in the Reaction of *cis*- and *trans*-3-*tert*-Butyl-7,7-dibromobicyclo[4.1.0]heptane with Methyllithium[1]

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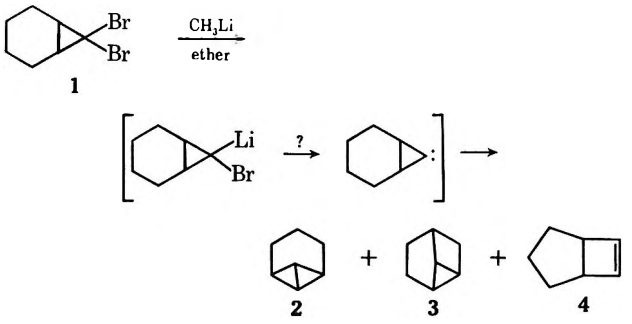
Addition of dibromocarbene to 4-*tert*-butylcyclohexene gives a mixture of 57% *cis*- and 43% *trans*-3-*tert*-butyl-7,7-dibromobicyclo[4.1.0]heptane (**7**). The treatment of *cis*-**7** with methyllithium leads to an intramolecular carbenoid insertion reaction which gives products (**9**, **11**, **12**) which are different from the products (**8**, **10**, **13**) obtained from *trans*-**7**. This result establishes that the stereoisomeric cyclopropylidene intermediates derived from *cis*- and *trans*-**7** do not interconvert and precludes the possibility of reversible opening of the cyclopropylidenes to 5-*tert*-butyl-1,2-cycloheptadiene. The six-membered ring of each cyclopropylidene must assume a half-chair conformation in which the *tert*-butyl group is equatorial. This conformation leads to selective insertion into either of the two axial C–H bonds which are cis to the carbenoid atom of the cyclopropylidene. The selectivity which is observed indicates that a tertiary C–H bond is substantially more reactive than a stereochemically comparable secondary C–H bond.

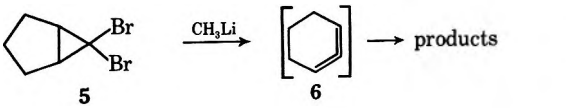
Many lines of recent evidence indicate that gem dihalides react with organolithium reagents to produce carbenoid intermediates which subsequently undergo a variety of reactions.[3] *gem*-Dibromocyclopropanes represent one of the more useful types of dihalides which serve as precursors for carbenoid intermediates. Thus, most *gem*-dibromocyclopropanes react with methyllithium to afford allenes in excellent yields,[4,5] either directly from an α-bromocyclopropyllithium intermediate or from rearrangement of the cyclopropylidene which would be derived from the former by loss of lithium bromide. In those cases where allenes are formed, no carbene or carbenoid intermediates have been trapped intermolecularly by olefins,[6] but Skattebøl[7] has reported the successful intramolecular trapping of several such intermediates with the formation of a number of interesting spiropentanes (tricyclic compounds).

In the systems which would lead to a highly strained allene, products derived from the carbene or carbenoid intermediates are found. Thus we have shown that the reaction of 7,7-dibromobicyclo[4.1.0]heptane (**1**) with methyllithium yields a variety of products which are indicative of a carbene or carbenoid intermediate.[4a,8] The mixture of the three hydrocarbons **2**, **3**, and **4** which result from intramolecular insertion can be obtained in 40–50% yield.[9] In addition, insertion on



the solvent, formation of a (formal) dimer of the cyclopropylidene, and trapping of the intermediate(s) with olefins to form spiropentanes stereospecifically all point toward the intermediacy of a carbene or carbenoid intermediate.[4a,8]

Although the products obtained from 7,7-dibromobicyclo[4.1.0]heptane clearly must have been derived from a carbene or carbenoid, it appeared to us that in small cyclic systems the cyclopropylidene and strained allene might interconvert. Marquis and Gardner[10] have found that 8,8-dibromobicyclo[5.1.0]octane reacts with methyllithium to give 1,2-cyclooctadiene and its dimer as well as carbene insertion products. In this case the strain in the cyclic allene presumably has diminished to the point where its formation is not prohibitive. Since 1,2-cycloheptadiene must be much more highly strained than 1,2-cyclooctadiene, intervention of the seven-membered-ring allene in reactions of 7,7-dibromobicyclo[4.1.0]heptane may seem out of the question, but we have found that 6,6-dibromobicyclo[3.1.0]hexane (**5**) reacts with methyllithium to give *exclusively 1,2-cyclohexadiene* (**6**), which sub-



sequently leads to dimers and tetramers.[11] With this fact in mind, it seemed entirely possible that cyclopropylidene–allene *interconversion* might occur prior

(1) Acknowledgment is made to the donors of the Petroleum Research Fund Administered by the American Chemical Society (1549-A4) and to the National Science Foundation (GP1306) for support of this research.

(2) National Institutes of Health Predoctoral Fellow, 1962–1965.

(3) (a) G. Kobrich, *Angew. Chem., Int. Ed. Engl.*, **6**, 41 (1967); (b) W. Kirmse, "Carbene, Carbenoide und Carbenanaloge," Verlag Chemie, Weinheim/Bergstr., Germany, 1969.

(4) (a) W. R. Moore and H. R. Ward, *J. Org. Chem.*, **25**, 2073 (1960); (b), W. R. Moore and H. R. Ward, *ibid.*, **27**, 4179 (1962); (c) L. Skattebøl, *Tetrahedron Lett.*, 167 (1961).

(5) Tetrasubstituted *gem*-dibromocyclopropanes are exceptions; intramolecular insertion products are formed. (a) W. R. Moore, K. Grant Taylor, P. Müller, Stan S. Hall, and Z. L. F. Gaibel, *ibid.*, 2365 (1970); (b) L. Skattebøl, *ibid.*, 2361 (1970); (c) W. R. Moore and J. B. Hill, *ibid.*, 4343 (1970).

(6) (a) 2,2-Diphenylcyclopropylidene has been trapped with olefins in the base-catalyzed decomposition of nitrosourea and urethane precursors of 2,2-diphenyldiazomethane: W. M. Jones, *J. Amer. Chem. Soc.*, **82**, 6200 (1960), and subsequent papers in this series. (b) Treatment of 2,2-dibromo-1,1-diphenylcyclopropane with methyllithium, a reaction which must involve the related carbenoid, is reported[4c] to give only 1,1-diphenylallene; no olefin trapping products were detected.

(7) L. Skattebøl, *J. Org. Chem.*, **31**, 2789 (1966).

(8) W. R. Moore, H. R. Ward, and R. F. Merritt, *J. Amer. Chem. Soc.*, **83**, 2019 (1961).

(9) A typical product ratio of **2**:**3**:**4** is ~96:4:3. The formation of compound **4** and related compounds in other systems (always minor) is significant in defining the mechanism of insertion; see ref 28.

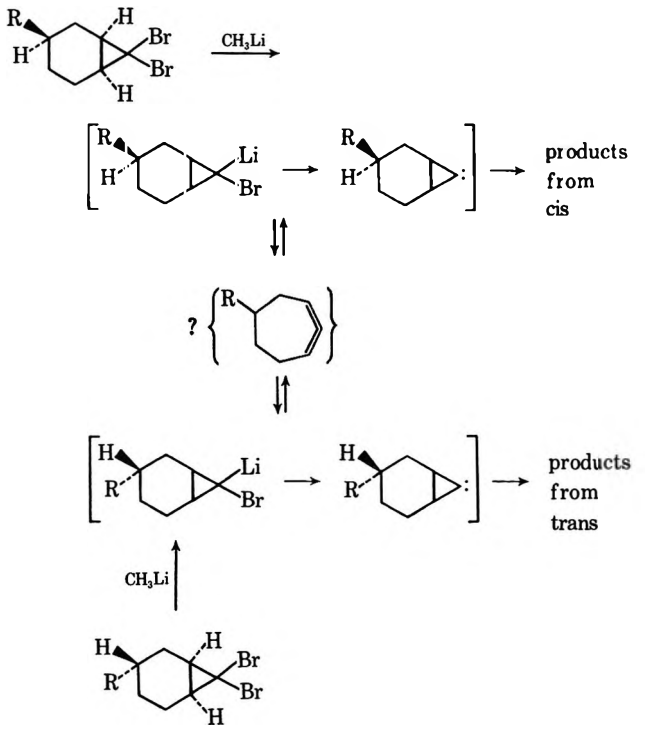
(10) E. T. Marquis and P. D. Gardner, *Tetrahedron Lett.*, 2793 (1966).

(11) W. R. Moore and W. R. Moser, *J. Amer. Chem. Soc.*, **92**, 5469 (1970).

to formation of the products from bicyclo[4.1.0]-heptylidene-7.

To examine this point, we elected to study the reactions of the cis and trans isomers of a 3-alkyl-7,7-dibromobicyclo[4.1.0]heptane. The principle is embodied in Scheme I. In the event that crossover

SCHEME I[a]



[a] All species are *dl*, only one enantiomer is shown.

products were observed, passage through a 1,2-cycloheptadiene would appear probable. At the outset, one must ask would failure to observe crossover products prove that a 1,2-cycloheptadiene was not an intermediate? On the basis of the arguments which follow, we believe that the answer to this question is clearly yes.

Three structural possibilities exist for 1,2-cycloheptadiene. (1) The diene could be described as being a "normal" (orthogonal) albeit highly strained allene. In this case the allene linkage would be somewhat twisted and bent and the other C–C–C bond angles would be distorted toward larger than normal values, all in the sense one finds upon constructing a simple model.[12] (2) The allene linkage could be planar with the three carbon atoms in that linkage still colinear. (3) The allene linkage could be planar and bent (nonlinear). In this case the structure would be similar to that proposed for 1,2-cyclohexadiene[11,13] and would resemble a 3-cycloheptenyl radical minus the C-2 hydrogen atom.[14]

In our system, the 3 substituent on the bicyclo-[4.1.0]heptane ring is *tert*-butyl, a bulky group which will be equatorial in the starting dibromides and carbene or carbenoid species derived from them. Each of the possible structures for 1,2-cycloheptadiene referred to above can exist in conformations which have clearly differentiated axial and equatorial positions at C-5 (equivalent to the C-3 positions of the reactants). Irrespective of the mechanism of ring opening, if a 1,2-cycloheptadiene is formed, the formation of the seven-membered ring can occur in a way which will retain the *tert*-butyl group in an equatorial conformation. Such a process must correspond to the lowest energy pathway; hence, it appears certain that it would be followed to a predominant extent. This line of reasoning leads to the conclusion that, if an allene intermediate were to be formed, both cis and trans bicyclic reactants would lead to the same equatorial 5-*tert*-butyl-1,2-cycloheptadiene which upon regenerating a cyclopropylidene would have to lead to crossover products.[15]

Results

The addition of dibromocarbene to a 4-alkylcyclohexene gives a mixture of the *cis*- and *trans*-3-alkyl-7,7-dibromobicyclo[4.1.0]heptanes in good yield, but the separation of the cis and trans isomers proved to be a major problem that dictated the course of the investigation. Thus 3-methyl-7,7-dibromobicyclo[4.1.0]-heptane appeared to be a single compound on more than 20 different (packed) glc columns; no separation was ever realized. Yet, reduction of the dibromide with sodium in liquid ammonia gave 3-methylbicyclo-[4.1.0]heptane which capillary glc showed was a 43:57 mixture of the cis and trans isomers (the stereochemistry was not assigned). Since the reduction would not affect the configuration of the C-3 methyl group, the dibromide must have been a similar mixture of isomers. Several other systems were examined, but only 3-*tert*-butyl-7,7-dibromobicyclo[4.1.0]heptane (**7**) proved to be suitable for this study. Dibromide **7**, obtained in 63% yield, could be partially resolved into the cis and trans isomers on 6 of 23 glc columns tried, the best giving a separation factor of only 1.04. Both glc and nmr analysis indicated a 43:57 ratio of isomers. Subsequent results established that the cis isomer predominated.[16] The slight preference for formation of the cis isomer must reflect subtle differences (not obvious) in steric hindrance of approach of dibromocarbene to the double bond.

Treatment of **7**[17] with methyllithium in ether at 0° gave a 62–66% yield of a mixture of isomeric hydrocarbons ($C_{11}H_{18}$) which were isolated by glc and shown to be the compounds indicated in Scheme II. All of the spectral properties of these compounds are in accord with the assigned structures.[18] Bicyclopentanes **10** and **11** show complex nmr patterns and infrared absorption in the C–H stretching region similar

(12) Framework Molecular Models, Prentice-Hall, Englewood Cliffs, N. J., probably give a representation as accurate as any.

(13) W. J. Ball and S. R. Landor, *J. Chem. Soc.*, 2298 (1962).

(14) While in principle these different possibilities exist for the structure of 1,2-cycloheptadiene, it clearly would be unreasonable to propose that the cis and trans systems could open to different types of allenes which did not interconvert.

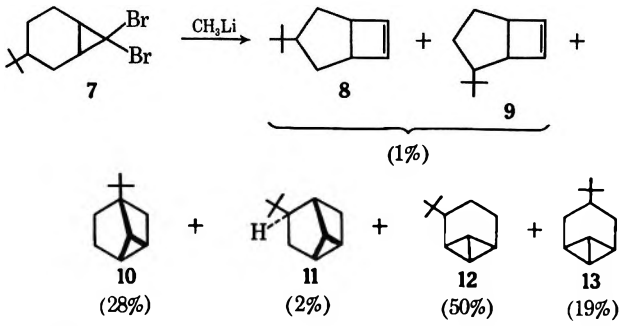
(15) A cis 3(*R*) and a trans 3(*R*) dibromide would lead to a common 5(*R*)-substituted 1,2-cycloheptadiene which subsequently could return to both cis and trans 5(*R*) bicyclic intermediates. It is immaterial whether or not return to one isomer (*e.g.*, *trans*) were favored, common products would be observed. It should be noted that this interconversion of cis and trans intermediates does not mean that the configuration at C-3 would be affected. If one were employing optically active reactants, even if crossover occurred, the products would be optically active.

(16) Reduction of **7** with sodium in liquid ammonia gave 3-*tert*-butylbicyclo[4.1.0]heptane. Although this material was not resolved on several glc columns, its nmr spectrum showed that it was also a mixture of isomers.

(17) All product isolation and identification was performed with the mixture of isomers.

(18) Full spectral data are given in the Experimental Section.

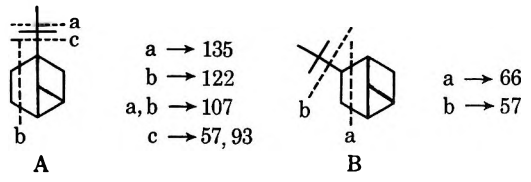
SCHEME II[a]



[a] Compounds are shown in order of increasing glc retention times.

to the spectra of **3**, and bicyclobutanes **12** and **13** show nmr signals and infrared absorption in the C–H stretching region similar to the spectra of **2**.

The mass spectra of **10** and **11** are strikingly different and are sufficient to define the structures (if not the stereochemistry of **11**). Thus **10** shows a fairly rich pattern which includes major peaks at *m/e* 57, 93 (base peak), 107, and 135 and a weak but significant peak at *m/e* 122, all of which can be readily accommodated by the fragmentations shown in structure A followed by straightforward rearrangements. In contrast, compound **11** shows a base peak at *m/e* 66, a major peak at *m/e* 57, and little else, a pattern which is clearly accounted for by the fragmentations shown in structure B.



The mass spectra of **12** and **13** are quite similar, showing dominant base peaks at *m/e* 57, but one significant difference is sufficient to distinguish between the 3 and 4 positions for the *tert*-butyl group. The molecular ion of **13** represents 2.90% of the sum of the intensities of all ions compared to only 1.33% for the molecular ion of **12**. Formation of a *tert*-butyl cation (*m/e* 57) clearly must be favored with the group in the 3 position, where bond cleavage will be directly facilitated by opening of the bicyclobutane ring.

Chemical evidence for the assignment of structures to **10**, **11**, **12**, and **13** as well as some transformations of these compounds appear in an accompanying paper.[19]

Compounds **8** and **9** emerged from the glc column ahead of the other compounds as two partially resolved peaks. Since these products were formed in such small amounts they were not extensively investigated, but, based on spectral data obtained on the mixture, it is clear that these peaks represent the 2- and 3-*tert*-butyl derivatives of **4**. Subsequent results indicate that **8** must have the *tert*-butyl group in the 3 position while **9** has a 2-*tert*-butyl group.[20]

In addition to the $C_{11}H_{18}$ hydrocarbons, higher boiling materials (much longer retention times) were also formed. These compounds were not investigated, but it seems safe to assume that they correspond to the high-boiling products formed from **1**[4a] and thus represent insertion into ether and (formal) dimerization of the $C_{11}H_{18}$ carbenoid intermediates.

The determination of whether or not *cis*- and *trans*-**7** led to different product spectra was made difficult because the partial separation of the isomeric dibromides achieved on analytical glc columns was diminished on preparative scale columns. However, employing glc and microreaction techniques appropriate to the problem, we established that the isomers of **7** did behave differently. The minor (trans) dibromide gave compounds **8**, **10**, and **13** while the major (cis) isomer gave compounds **9**, **11**, and **12**. In each case the reactions are at least 98% stereospecific.

The assignment of stereochemistry to the isomers of **7** is established by these results. Compound **10** can be formed only from the trans dibromide and compound **11** must come from the cis isomer.

The influence of the reaction temperature and the source of the methyllithium used in the reaction on the relative and total yields of the insertion products obtained from the 57:43 mixture of *cis*- and *trans*-**7** was investigated. When methyllithium is prepared from a methyl halide in ether the lithium halide which is formed remains in solution;[21] in our case, the reagent contained either lithium bromide or lithium iodide.[22] In some cases the lithium halide can have a significant effect, either by changing the nature of the carbenoid precursor or by being involved in some other way in the transition states of the subsequent reactions.[23] The results, summarized in Table I, show that the relative yields are nearly independent of the presence or absence of lithium iodide. The most important effect is the large decrease in the total yield at −80°, particularly when lithium iodide is present. In other systems, we have established that the yields of the dimeric products increase when lithium iodide is employed at −80°.[24] Accordingly, glc analysis showed an increase in the formation of high-molecular-weight products believed to be dimers.

Discussion

The stereospecificity in the reaction of *cis*-**7** and *trans*-**7** with methyllithium establishes that a 1,2-cycloheptadiene is not an intermediate en route to the intramolecular insertion products. We can see no reason why the presence of the 3 substituent would have any substantial effect on the ease of opening of the three-membered ring. Hence, we conclude that in general a cyclopropylidene incorporated into a bicyclo[4.1.0]-heptane system does not experience opening and reclosure prior to undergoing C–H insertion. Since the next higher and lower homologs *do open*, the failure of the [4.1.0] system to open may seem anomolous. The fact that the [5.1.0] system does undergo partial ring opening to form 1,2-cyclooctadiene[10] means that, al-

(19) W. R. Moore and B. J. King, *J. Org. Chem.*, **36**, 1882 (1971).

(20) See ref 28. In other systems we have also isolated derivatives of **4** as minor products.

(21) Cooling such solutions causes precipitation of some, but not all, of the lithium halide.

(22) In other studies we have found that employing halide-free methyllithium gives the same results as using methyllithium-containing lithium bromide, presumably because lithium bromide is formed in the reaction: W. R. Moore and C. Kandall, unpublished results.

(23) (a) M. G. Goldstein and W. R. Dolbier, *J. Amer. Chem. Soc.*, **87**, 2293 (1965); (b) G. Closs and C. H. Lin, 20th National Organic Chemistry Symposium of the American Chemical Society, Burlington, Vt., June 1967.

(24) W. R. Moore and M. McGrath, unpublished results.

TABLE I

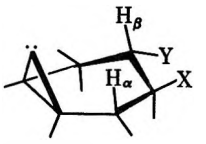
YIELDS OF INTRAMOLECULAR INSERTION PRODUCTS FROM THE 57:43 MIXTURE OF *cis*- AND *trans*-7

Lithium halide	Temp, °C	Percentage of total[a] 8	9	10	11	12	13	Total yield, %
LiBr	0	0.6	0.8	27.9	2.3	49.7	18.7	62
LiI	0	0.5	0.5	28.6	1.9	49.9	18.6	66
LiBr	−80	0.4	0.6	24.7	1.3	52.9	20.1	38
LiI	−80	0.1	0.4	29.6	1.4	51.5	17.0	28
Uncertainty[b]		±0.1	±0.1	±0.6	±0.2	±0.6	±0.4	±2

[a] Each entry represents the mean of the four values obtained from duplicate runs, each run being analyzed twice by glc. [b] The uncertainty represents the 95% confidence interval calculated on the basis of $N = 4$ employing standard deviations determined from the pooled results.

though this allene is certainly strained,[25] and the opening is clearly slowed, the strain is not sufficently high, or at least the extent to which this developing strain is felt at the transition state is not sufficient, to preclude opening in the same sense that is found for most other cyclopropylidenes. The [3.1.0] system leads to 1,2-cyclohexadiene, a planar allene, but the reaction may not involve opening of a cyclopropylidene;[11] rather the α-bromocyclopropyllithium intermediate may rearrange in a manner which is analogous to the carbonium ion rearrangements found for endo-6-substituted derivatives of bicyclo[3.1.0]hexane, rearrangements which are facile because of relief of strain.[26] The bicyclo[4.1.0]-heptane system must lie in a structural region for which opening in the conventional sense to an orthogonal allene is denied because the allene would be too highly strained and yet opening to a planar allene is not favored, primarily because the [4.1.0] system lacks the added strain present in the [3.1.0] system.

In addition to establishing that a 1,2-cycloheptadiene is not an intermediate,[27] the results also provide information concerning the process of intramolecular insertion. The cyclopropylidene intermediates must have half-chair conformations with the *tert*-butyl groups equatorial and thus can be represented as **14** and **15** (shown as "free carbenes" for simplicity). In these conformations, insertion can only occur into the axial C–H bonds indicated as H_α and H_β; as models will show, all equatorial positions are clearly much too far from the carbenoid center to permit insertion. Hence **14** would be expected to give only **11** and **12**, while **15** would be expected to give only **10** and **13**.[28] The fact that this selectivity is *observed experimentally* establishes that these half-chair conformations must correctly describe the systems.



14(cis), X = *tert*-Bu; Y = H
15(trans), X = H; Y = *tert*-Bu

Given that intramolecular insertion occurs from conformations **14** and **15**, it is clear that the H_α/H_β selectivity, equivalent to bicyclobutane *vs.* bicyclopentane formation, is drastically different for the two systems. At 0° (lithium bromide) the *cis*-cyclopropylidene **14** gives a ratio of 22 to 1 for bicyclobutane **12** to bicyclopentane **11**, approximately the same as the ratio of bicyclobutane **2** to bicyclopentane **3** obtained when the unsubstituted dibromide **1** was treated with methyllithium.[8,c] On the other hand, the *trans*-cyclopropylidene **15** gives a ratio of 1 to 1.5 for bicyclobutane **13** to bicyclopentane **10**. Clearly in the cis system, the *tert*-butyl group does not affect the relative reactivities of H_α and H_β, indicating that it does not cause appreciable distortion of the conformation compared to that of the unsubstituted compound. On this basis, it would appear that the 33-fold enhancement of the reactivity of H_β relative to H_α in the trans system does not, at least for the most part, result from distorting the normal half-chair conformation in a way which would move H_β toward and H_α away from the carbenoid center. These motions would result if the *tert*-butyl group of **15** were to rock up toward the carbenoid center. However, it is not apparent why such twisting should occur in **15** but not in **14**. Thus the enhanced selectivity of insertion into the C–H_β bond of **15** must result primarily from the electronic effect of the *tert*-butyl group.[29] The C–H_β bond of **15** is tertiary, whereas all other C–H bonds involved in insertion in **14** and **15** are secondary and in general one anticipates a reactivity order for C–H bonds of tertiary > secondary > pri-

(25) 1,2-Cyclooctadiene must have a "conventional" structure; *i.e.*, it must have an orthogonal allenic linkage which is probably slightly twisted.

(26) (a) J. Sonnenberg and S. Winstein, *J. Org. Chem.*, **27**, 748 (1962); (b) U. Schöllkopf, K. Fellenberger, M. Patsch, P. v. R. Schleyer, T. Su, and G. W. van Dine, *Tetrahedron Lett.*, 3639 (1967); (c) U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, **7**, 588 (1968).

(27) The results also exclude organometallic species, such as 2-lithio-3-bromocycloheptene or a lithium bromide complex of 1,2-cycloheptadiene, having the same carbon skeleton symmetry as the allene from being intermediates.

(28) The formation of bicyclo[3.2.0]hept-6-ene derivatives is also selective; *cis*-**7** gives **9** and *trans*-**7** gives **8**. This selectivity allows assignment of the position of the *tert*-butyl group in **8** and **9** as follows. Bicyclo[3.2.0]-hept-6-ene (**4**) can be regarded as a "valence" isomer of tricyclo[4.1.0.$0^{2,7}$]-heptane (**2**). It appears to be derived from insertion commencing in the same sense as that leading to **2** (*i.e.*, the shift of the H atom occurs from C-2 to C-7) followed at some point by carbon–carbon bond shifts resulting in rearrangement to **4**. Irrespective of the timing of these shifts the C-1,5 bond of **4** must join what would be the C-2 and C-6 positions of **1**. Applying these considerations to the present substituted case, it becomes clear that the "valence" isomer pairs must be **8**, **13** and **9**, **12**. Thus **8** is 3- and **9** is 2-*tert*-butylbicyclo[3.2.0]hept-6-ene. At this time it appears that **8** and **9** may be mixtures of the exo and endo isomers, but we cannot state with certainty that they are or are not. Since this point is of great importance in establishing the mechanism of formation of the [3.2.0] system, it is under investigation.

(29) From the data obtained from the mixture of 57% *cis*- and 43% *trans*-**7**, the yield of intramolecular insertion products is found to be about 57% from *cis*-**7** compared to 68% from trans-**7** (0°, LiBr). In each case the balance of the material appears as higher molecular weight products which result from intermolecular reactions. The latter reactions provide an internal standard of sorts since their rates should be independent of the stereochemistry of the *tert*-butyl group, which is sensibly remote from the carbenoid center. Thus the enhanced reactivity of C–H_β of **15** is reflected in a net increase in intramolecular insertion products. The fact that the yield of **8** + **13** is 28% based on *trans*-**7** while the yield of **9** + **12** is 55% based on *cis*-**7** does *not* mean that the C–H_α bond of the trans isomer is deactivated, but simply reflects the fact that the competitive insertion into the C–H bond of **15** is more efficient at removing a common intermediate.

mary.[30] This order stems from the ability of an alkyl group to supply electrons to the adjacent electron-deficient center in the transition state of the insertion reaction. Since the effect is large in this case, it indicates that these cyclopropylidenes are highly selective.

Experimental Section[31]

4-*tert*-Butylcyclohexene.—Treatment of 4-*tert*-butylcyclohexanol (Aldrich Chemical Co.) with acetic acid and acetic anhydride gave 4-*tert*-butylcyclohexyl acetate in 96% yield, bp 75–78° (1 mm).

The acetate was pyrolyzed by passing it through a glass helices packed column heated to 570°. Following the usual work-up, distillation afforded an 81% yield of 4-*tert*-butylcyclohexene, bp 66° (20 mm), n^{17}D 1.4606 [lit.[32] bp 65–66° (20 mm), n^{20}D 1.4583]. Glc analysis showed only one peak on Versamide 900, Carbowax 20M, and SE-30. The infrared spectrum showed no bands at 1035 or 996 cm^{-1} (bands reported to be in 1- and 3-*tert*-butylcyclohexene respectively); [33]nmr δ 0.83 (s, 9 H), 1.25 (broad m, 3 H), 1.6–2.3 (4 H), 5.68 (broad s, 2 H).

3-*tert*-Butyl-7,7-dibromobicyclo[4.1.0]heptane (7).—A pentane solution of 4-*tert*-butylcyclohexene was slurried with potassium *tert*-butoxide and freshly distilled bromoform was added dropwise while cooling to 0°. After the usual work-up, distillation gave a 63% yield of 7: bp 96° (0.35 mm); n^{26}D 1.5298; ir (CCl_4) 3000, 2960, 2860, 1476, 1440, 1400, 1370, 1240, 1050 cm^{-1}; nmr δ 0.80 (s, 3.9 H), 0.84 (s, 5.1 H), 0.9–2.2 (complex, 9 H). *Anal.* Calcd for $C_{11}H_{18}Br_2$: C, 42.61; H, 5.85; Br, 51.54. Found: C, 42.74; H, 5.77; Br, 51.52.

Of all the glc columns shown in footnote 31 (except the last three which were not tried), only LAC 2-R-446, LAC-1-R-296 SAIB, Hyprose, UCON polar, and CPS showed partial separation of the two isomers. A 350 × 0.4 cm 10% Craig polyester succinate column at 140° (showing 3600 theoretical plates) gave the best partial separation; the retention time ratio was cis/trans = 1.04. Employing analysis of the peak shapes, the peaks were resolved graphically to enable a determination of the cis:trans ratio, found to be 57:43. This ratio is confirmed by the nmr spectrum in which the same ratio was seen for the *tert*-butyl peaks.

Unfortunately, preparative separation by glc was made very difficult because the peaks broadened and merged when the sample size was increased (analytical measurements employed a flame ionization detector and very small samples). By repeated collection of the front and back of the merged peak, it was possible to obtain samples of the order of 1 mg which were enriched in the trans and cis isomers but were not pure. In order to obtain each isomer as pure as possible, small glc samples were employed and only *ca.* 1% of the extreme front and rear of the merged peak was collected, affording quantities of the individual isomers estimated to be *ca.* 0.01 mg.

3-*tert*-Butylbicyclo[4.1.0]heptane.—Reduction of 7 with sodium in liquid ammonia followed by work-up and distillation gave 3-*tert*-butylbicyclo[4.1.0]heptane: bp 72° (21 mm); nmr δ −0.1 (m, 1 H), 0.2–2.4 (broad and complex, 19 H, but with two *tert*-butyl singlets totaling 9 H at 0.78 and 0.80 having a ratio similar to that for 7); mass spectrum *m/e* 152 (M^+). Although this material was definitely a mixture of isomers based on the nmr spectrum, it gave a single peak on several glc columns. *Anal.* Calcd for $C_{11}H_{20}$: C, 86.76; H, 13.24. Found: C, 86.88; H, 13.04.

Reaction of 7 with Methyllithium.—Methyllithium (0.020 mol) in ether was added to a solution of 5.0 g (0.016 mol) of 7 in 20 ml of ether maintained at 0°. Water was added and the ether layer was separated and dried (Na_2SO_4). The volatile materials were distilled at 25° (0.05 mm) into a trap maintained at −78°. The distillate was concentrated by distillation using a 26 × 1 cm Vigreux column. Glc analysis (350 × 0.2 cm, 2% Carbowax 20M on basic Chromosorb P, 98°) showed the six-component mixture with the following retention times relative to *p*-xylene (1.00): **8** (1.30), **9** (1.40), **10** (1.63), **11** (1.74), **12** (2.17), **13** (2.54). The compounds were collected from preparative glc columns; spectral and analytical data are presented later. In order to prevent rearrangment of the bicyclobutanes which are very sensitive to acids, it was absolutely imperative to wash all glassware with alkaline methanol, to use base-washed glc supports, and to use either on-column injection or clean inserts in the inlet system of the glc instruments.

The nonvolatile residue from the distillation was analyzed by glc (SE-30, 90 → 240°) showing that it was a complex mixture of products with retention times similar to that of the starting dibromide. This material was not investigated further.

The reaction was repeated employing 1 mmol of 7 in 6 ml of ether. Methyllithium prepared from both methyl bromide and methyl iodide was used and reaction temperatures were maintained at 0 and −80°. The reaction mixture was analyzed directly after hydrolysis (without distillation) employing *p*-xylene as an internal standard. In each case duplicate runs were made and each reaction mixture was analyzed twice. The averages of these determinations are given in Table I.

In order to carry out the reaction reproducibly on a very small scale, the following technique was employed. A melting point capillary sealed at one end was placed in a 10 × 1.5 cm glass tube also sealed at one end. After both tubes had been dried at 160°, they were flushed with nitrogen and the outer tube was sealed while warm with a "No-Air" stopper. The apparatus was cooled and 0.5 ml of 0.5 *M* methyllithium in ether was injected (syringe) into the outer tube to serve as a drying agent and oxygen scavenger. If the solution did not turn cloudy, *ca.* 2 μl of 7 was injected (microliter syringe) into the inner tube. The apparatus was cooled to 0° and 50 μl of 0.5 *M* methyllithium solution was injected (microliter syringe) into the inner tube. The reaction mixture was allowed to warm to room temperature and then was analyzed directly by glc (Carbowax 20M). On-column injection was employed utilizing a replaceable section at the front of the column (which served to hydrolyze excess methyllithium). Using the 53:47 mixture of *cis*- and *trans*-7 and methyllithium prepared from methyl bromide, this procedure was found to give results (the average of nine reactions) which were indistinguishable from those in Table I. Employing several 0.5–1-mg samples of 7 collected by glc and enriched in either isomer led to enrichment in the $C_{11}H_{18}$ products in the sense indicated previously. With the very small samples of 7 (*ca.* 0.01 mg, transferred from the glc collectors with a few microliters of ether), 10 μl of methyllithium was used and the entire reaction mixture was injected in one pass in the glc analysis. These reactions established a lower limit of 98% in the stereospecificity based on the estimated detection limits.

2- and 3-*tert*-Butylbicyclo[3.2.0]hept-6-ene (8 and 9).—The mixture (*ca.* 1:1) was collected by glc employing an XE-60 column: ir (CCl_4) 3025, 2950, 2860, 1720, 1470, 1390, 1365 cm^{-1}; nmr (CCl_4) δ 0.81, 0.89, 0.94 (three s, ~9 H, *tert*-butyl) superimposed on 0.8–2.3 complex multiplet (~5 H), 3.2 (d, 2 H), 5.85 (s, 2 H); mass spectrum *m/e* (rel intensity) 150 (M^+, 0.5), 135 (4), 107 (7), 94 (15), 93 (27), 91 (14), 80 (27), 79 (28), 77 (15), 57 (100), 55 (11), 41 (38), 39 (23).

5-*tert*-Butyltricyclo[3.2.0.0^{2,7}]heptane (10).—The compound was collected by glc employing a Carbowax 20M column: ir (neat) 3050, 3030, 2955, 2900, 2865, 1475, 1395, 1365, 1325, 1220, 1245, 1180, 1118, 962, 915, 895, 840, 810, 800, 770, 725, 690 cm^{-1}; nmr (CCl_4) δ 0.94 (s, 9 H), 1.06 (d, 1 H), 1.2–1.45 (m, 3 H), 1.45–1.8 (m, 1 H), 1.8–2.3 (m, 4 H); mass spectrum *m/e* (rel intensity) 150 (M^+, 3), 135 (58), 122 (3), 107 (37), 94

(30) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 55.

(31) Infrared spectra were determined with Perkin-Elmer Models 237 and 337 spectrophotometers. Nmr spectra were obtained on a Varian A-60 spectrometer. Mass spectra were determined on a Consolidated Electrodynamics Model 21–130 mass spectrometer with an ionizing potential of 68 V (inlet system heated to 135°). The gas chromatography apparatus utilized thermal conductivity detectors (homemade, all glass) or flame ionization detectors with (F & M Model 810) or without (Wilkins Model A-600) a carrier gas stream splitter. Columns were 300–350 × 0.2 cm for analytical (2–10% liquid phase) and 200–350 × 1.0–1.4 cm (10–20% liquid phase) for preparative purposes. Liquid phases employed (on neutral or basic Chromosorb P) were Carbowax 20M, silicone nitrile (XF-1150), silicone nitrile (XE-60), Craig polyester succinate (CPS), SE-30 silicone rubber, ethylene glycol adipate, Versamide 900, silicone 200, LAC-2-R446, LAC-1-R296, Tide (40–60 mesh), sucrose acetate isobutyrate (SAIB), Hyprose, "air-blown" asphalt, *m*-bis(diphenoxy)benzene, tricresylphosphate, UCON Polar, tricyanoethoxypropane (TCEP), tetraethylene glycol (TEG), 3-nitro-3-methylpimelonitrile (NMPN), and silver nitrate–ethylene glycol. Gas chromatographic analyses employed internal standards utilizing appropriate response factors with peak areas determined by planimetering. Elemental analyses were performed by Dr. S. M. Nagy and associates at the Massachusetts Institute of Technology. All melting points and boiling points are uncorrected. All reactions employing organometallic reagents, active metals, alkoxides, or hydrides were conducted under a nitrogen atmosphere.

(32) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5577 (1955).

(33) H. L. Goering, R. L. Reeves, and H. H. Espy, *ibid.*, **78**, 4926 (1956).

(37), 93 (100), 92 (13), 91 (32), 83 (12), 81 (12), 79 (37), 77 (27), 67 (10), 65 (10), 57 (63), 55 (28), 53 (13), 43 (16), 41 (58), 39 (38). *Anal.* Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.07. Found: C, 88.10; H, 12.03.

exo-4-*tert*-Butyltricyclo[3.2.0.0^{2,7}]heptane (11).—The compound was collected by glc employing an XF-1150 column: ir (CCl_4) 3055, 3030, 2960, 2900, 2856, 1470, 1395, 1365, 1300, 1245, 1210, 1075, 955, 890 cm^{-1}; nmr (CCl_4) δ 0.80 (s, 9 H), 0.8–1.7 (m, 4 H), 1.7–2.15 (m, 4 H), 2.15–2.6 (m, 1 H); mass spectrum *m/e* (rel intensity) 150 (M^+, 1) 135 (2), 107 (5), 93 (6), 91 (7), 79 (9), 77 (7), 69 (9), 67 (8), 66 (100), 57 (33), 41 (20), 39 (11).

3-*tert*-Butyltricyclo[4.1.0.0^{2,7}]heptane (12).—The compound was collected by glc employing a Carbowax 20M column: ir (CCl_4) 3083, 2990, 2960, 2860, 1475, 1393, 1365, 1238, 1225, 1130, 975 cm^{-1}; nmr (CCl_4) δ 0.88 (s, 9 H, *tert*-butyl), 1.51 (t, 2 H, C-1,7) superimposed on 0.9–1.6 (broad m, 5 H), 2.36 (m, 2 H, C-2,6); mass spectrum *m/e* (rel intensity) 150 (M^+, 5) 135 (4) 107 (2), 94 (48), 93 (14), 91 (12), 79 (29), 77 (13), 57 (100), 41 (31), 39 (16). *Anal.* Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.07. Found: C, 88.08; H, 12.06.

4-*tert*-Butyltricyclo[4.1.0.0^{2,7}]heptane (13).—The compound was collected by glc employing a Carbowax 20M column: ir 3090, 2995, 2960, 2860, 1475, 1390, 1365, 1290 (d), 1240, 1175, 1135, 1060, 980 cm^{-1}; nmr (CCl_4) δ 0.78 (s, 9 H, *tert*-butyl), 1.46 (t, 2 H, C-1,7) superimposed in 0.8–1.3 (broad m, 5 H), 2.34 (m, 2 H, C-2,6); mass spectrum *m/e* (rel intensity) 150 (M^+, 12), 135 (4), 107 (9), 94 (25), 93 (18), 91 (14), 79 (28), 77 (12), 57 (100), 41 (20), 39 (15). *Anal.* Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.07. Found: C, 88.09; H, 12.09.

The nmr spectra of **12** and **13** did not change significantly when taken in chloroform, benzene, pyridine, or methanol.

3-Methyl-7,7-dibromobicyclo[4.1.0]heptane.—Commercial 4-methylcyclohexene (Eastman Kodak White Label) was found to contain 11% of isomeric impurities, mainly 3-methylcyclohexene, as shown by glc analysis on an ethylene glycol–silver nitrate column. Hence 4-methylcyclohexyl acetate was prepared and pyrolyzed[34] at 570° to give 4-methylcyclohexene in 80% yield, n^{24}D 1.4389 (lit.[34] n^{20}D 1.4414), which was shown by glc to be free of isomers.

Dropwise addition of 253 g (1 mol) of bromoform to a cold slurry (both at −15°) of 1 mol of potassium *tert*-butoxide, 29 g (0.96 mol) of 4-methylcyclohexene, and 500 ml of pentane followed by the usual work-up gave 144 g (54%) of 3-methyl-7,7-dibromobicyclo[4.1.0]heptane: bp 62–64° (0.25 mm); n^{26}D 1.5419; ir 2970, 2900, 2820, 1445, 1380, 1335, 1460 cm^{-1}. *Anal.* Calcd for $C_8H_{12}Br_2$: C, 35.85; H, 4.51; Br, 59.63. Found: C, 36.02; H, 4.59; Br, 59.68.

All attempts to crystallize this dibromide at low temperatures failed. Glc in all columns listed in footnote 31 except the last three (not tried) showed only one peak.

Reduction of the dibromide with sodium in liquid ammonia employing ether as a cosolvent followed by the usual work-up gave 3-methylbicyclo[4.1.0]heptane, collected by glc (silicone 200, to remove a 6% impurity), mass spectrum *m/e* 110 (M^+). Analysis of this material in a 60-m polyethylene glycol capillary glc column[35] showed two peaks with very close retention times in an area ratio of 43:57.

Addition of the Simmons–Smith reagent[36] to 4-methylcyclohexene gave 3-methylbicyclo[4.1.0]heptane having a mass spectrum identical with that of the sample obtained from reduction of the dibromide. Capillary column glc analysis showed the same two peaks in an area ratio of 44:56.

Registry No.—*cis*-**7**, 29339-16-0; *trans*-**7**, 29339-17-1; **8**, 29339-18-2; **9**, 29339-19-3; **10**, 29339-20-6; **11**, 29339-21-7; **12**, 29488-51-5; **13**, 29339-23-9; methyllithium, 917-54-4; 3-methyl-7,7-dibromobicyclo[4.1.0]heptane, 29339-24-0; *cis*-3-*tert*-butylbicyclo[4.1.0]heptane, 29339-25-1; *trans*-3-*tert*-butylbicyclo[4.1.0]heptane, 29339-26-2.

(34) E. Gil-Av, J. Herling, and J. Shabtai, *J. Chromatogr.*, **1**, 508 (1958).

(35) We are indebted to Dr. E. P. Blanchard, Jr., of the E. I. du Pont de Nemours and Co., Inc., for the capillary column analyses.

(36) R. D. Smith and H. E. Simmons, *Org. Syn.*, **41**, 72 (1961).

Derivatives of Bicyclobutane and Bicyclo[2.1.0]pentane. Establishment of the Structures of 3- and 4-*tert*-Butyltricyclo[4.1.0.0^{2,7}]heptane and 5- and *exo*-4-*tert*-Butyltricyclo[3.2.0.0^{2,7}]heptane[1]

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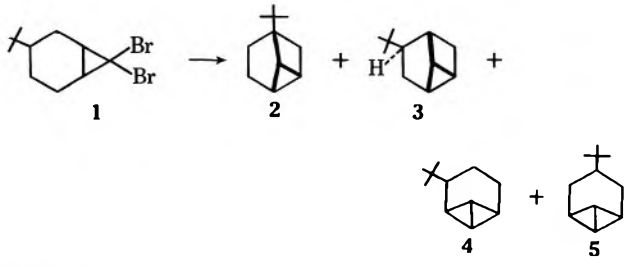
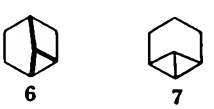
The structures of bicyclo[2.1.0]pentane derivatives **2** and **3** have been established by hydrogenation to **8** and **15**, respectively, compounds which were synthesized independently. Treatment of **2** with aluminum chloride resulted in rearrangment to an isomer assigned structure **11**. Bicyclobutane derivative **4** was isomerized by magnesium bromide in ether to **17**, **18**, and **19**, while **5** gave **20** and **21**. These results distinguish between **4** and **5** and, when product ratios are considered, provide a basis for suggesting how the rearrangements occur.

The treatment of a mixture of 57% *cis*- and 43% *trans*-3-*tert*-butyl-7,7-dibromobicyclo[4.1.0]heptane (**1**) with methyllithium produced four tricyclic hydrocarbons **2**, **3**, **4**, and **5**.[3] While the spectral properties of these products were sufficient to define **2** and **3** as *tert*-butyl derivatives of tricyclo[3.2.0.0^{2,7}]heptane (**6**) and **4** and **5** as *tert*-butyl derivatives of tricyclo[4.1.0.0^{2,7}]heptane (**7**), the position of the *tert*-butyl group



1 **2** **3** **4** **5**



6 **7**

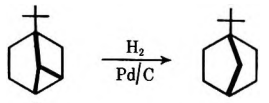
in each case was assigned solely on the basis of mass spectral data. Since our arguments really set, rather than rely on precedent, we undertook to define the structures chemically by unequivocal means and hoped that in the process we would establish some reaction patterns for these and related systems.

(1) Acknowledgment is made to the donors of the Petroleum Research Fund administered by the American Chemical Society (1549-A4) and to the National Science Foundation (GP 1306) for support of this research.

(2) National Institutes of Health Predoctoral Fellow, 1962–1965.

(3) W. R. Moore and B. J. King, *J. Org. Chem.*, **36**, 1877 (1971).

Bicyclopentane Derivatives 2 and 3.—It was found previously that 6 could be hydrogenated cleanly to norbornane over palladium on carbon.[4] Under similar conditions, 2 was hydrogenated readily to give a single product which we identified as 1-*tert*-butylnorbornane

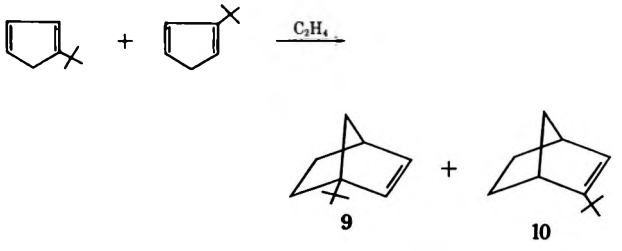


2 8

(8) on the basis of the nmr spectrum which, in particular, showed only one bridgehead proton as a broad singlet at δ 2.14.

To establish the structure of **8** unequivocally, we sought an alternate synthesis. Since several attempts to couple *tert*-butyl and 1-norbornyl derivatives failed, we turned to the synthesis of 1-*tert*-butylnorbornene (**9**).

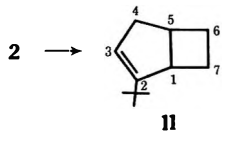
Perhaps surprisingly, sodium cyclopentadienide can be alkylated with *tert*-butyl bromide to give a modest yield of a mixture of 1- and 2-*tert*-butylcyclopentadiene.[5] This mixture was condensed with ethylene to give a 4:1 mixture of two adducts. The major product proved to be 2-*tert*-butylnorbornene (**10**). This ma-



9 10

terial was identical with the major product obtained from the acid-catalyzed dehydration of 2-*tert*-butyl-2-hydroxynorbornane,[6] prepared by adding *tert*-butyllithium to norcamphor. The minor product from the Diels–Alder reaction, identified as **9** on the basis of nmr and mass spectra, was hydrogenated to give a sample of **8** identical with that derived from 2.

In the course of establishing the structure of 2, we examined its behavior with aluminum chloride, since it seemed possible that it might rearrange to **9**. However, rather than **9**, the major product was an isomer assigned structure **11**. The nmr spectrum of **11** shows a triplet



11

at δ 5.41 for the olefinic proton and a nine-proton singlet at δ 1.07, a downfield shift which indicates that the *tert*-butyl group is attached to a double bond. The signals from the remaining eight "saturated" protons give rise to a series of multiplets centered at *ca.* δ 1.8–3.65, the downfield shifts being consonant with a structure in which the protons concerned are allylic, on a four-membered ring, or both, and, in some cases, tertiary as well.

(4) W. R. Moore, H. R. Ward, and R. F. Merritt, *J. Amer. Chem. Soc.*, **83**, 2019 (1961).

(5) R. Alder and H. J. Ache, *Chem. Ber.*, **95**, 503 (1962).

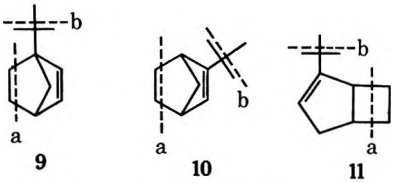
(6) We had hoped that **9** might be a product from this dehydration as a consequence of a Wagner–Meerwein rearrangement, but at most minor amounts of it were formed.

The mass spectrum of **11** also is highly informative. We have prepared a number of $C_{11}H_{18}$ hydrocarbons in this work and have found that, in general, the compounds give fragment peaks at about the same mass numbers, but the relative intensities of the peaks are usually quite different. However, the mass spectra of **9**, **10**, and **11** are *almost identical*. Furthermore, as can be seen in Table I, the spectra of all three compounds bear a striking similarity to that of the mixture of 1- and 2-*tert*-butylcyclopentadiene. These facts imply that loss of ethylene, as shown in structures **9**–**11**, must be the major primary fragmentation path for the three C_{11} compounds.[7]

TABLE I
MASS SPECTRA OF RELATED HYDROCARBONS

	Relative intensities			
m/e	**9**	**10**	**11**	*tert*-Butylcyclopentadiene[a]
150	2.5	6	1.5	
135	2	3	3	
122	33	25	25	24
107	100	100	100	100
91	12	17	12	52
79	9	9	9	16
77	7	8	7	10
65	6	5	6	11
57	33	29	32	38

[a] A mixture of 2- and 3-*tert*-butylcyclopentadiene was used.



a ⟶ *m/e* 122
a,b ⟶ *m/e* 107

While the mass spectral data clearly establish the bicyclo[3.2.0]hept-2-ene system, they do not distinguish between the 2 and 3 positions for the location of the *tert*-butyl group. However, the nmr signal from the olefinic proton assigned to C-3 of **11** is a triplet due to modest coupling ($J \sim 2$ Hz) with the C-4 methylene group and, as shown by double resonance techniques, coupling to the C-1 proton is very small. These facts provide a rational basis for assigning the *tert*-butyl group to C-2.[8]

The rearrangement of 2 to **11** can be viewed as opening[9a] of the highly strained 1,7 bond to give cation **12**, followed by rearrangement to **13** and loss of a proton. Since **9** is not formed (*via* a 4-*tert*-butylnorborn-

(7) Mass spectra were determined with a 360° cycloidal instrument which precluded measurement of metastable peaks; *cf.* K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, p 157.

(8) We wish to thank Paul D. Mogolesko and Stephen D. Clark for 100-MHz spectra and carrying out the double resonance experiments.

(9) (a) Although aluminum chloride was the catalyst and one could formulate the rearrangement in terms of an intramolecular hydride shift from C-6 to C-7, it is more likely that a trace of hydrogen chloride served as a proton transfer agent. (b) This pathway is similar to the rearrangment of certain bicyclo[2.2.1]heptane derivatives to [3.2.0] systems: S. Winstein and E. T. Stafford, *J. Amer. Chem. Soc.*, **79**, 505 (1957); E. E. van Tamelen and C. I. Judd, *ibid.*, **80**, 6305 (1958).

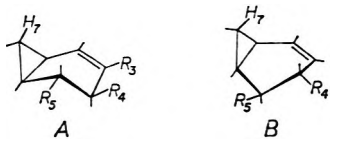
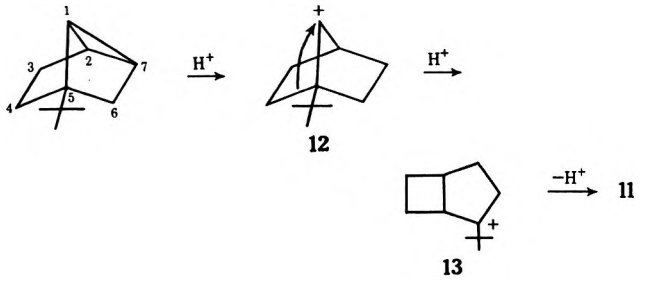
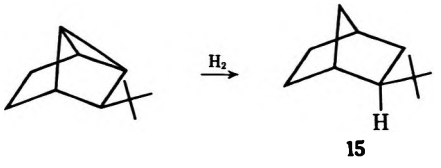


Figure 1.—Conformations of bicyclo[4.1.0]hept-2-enes. A (class A): **16**, $R_3 = R_4 = R_5 = H$; **18**, R_3 = *tert*-Bu, $R_4 = R_5 = H$; **19**, $R_3 = R_4 = H$, R_5 = *tert*-Bu; **21**, $R_3 = R_5 = H$, R_4 = *tert*-Bu. B (class B): **17**, $R_4 = H$, R_5 = *tert*-Bu; **20**, R_4 = *tert*-Bu, $R_5 = H$.

2-yl cation), the rearrangement of **12** to **13** may be concerted with opening of the three-membered ring.[9b]



Hydrogenation of **3** gave a single product which has been identified as *exo*-2-*tert*-butylnorbornane (**15**).



The Cu(I)-catalyzed coupling of the Grignard reagent prepared from *exo*-2-chloronorbornane[10] with *tert*-butyl chloride gave as the major C_{11} product a compound identical with that obtained from hydrogenation of **3**. On steric grounds, one would expect that the exo isomer would form preferentially in the coupling reaction. In addition, these samples of 2-*tert*-butylnorbornane have nmr spectra identical with that reported for the product of the addition of *tert*-butyllithium to norbornene, which, also on steric grounds, has been assigned the exo configuration.[11] These exo assignments were confirmed by our observation that reduction of **10** with diimide gave an isomer of **15**. Since diimide gives cis addition from the less-hindered side of a double bond,[12] this product clearly is the endo isomer. The same product was obtained upon hydrogenation of **10** over palladium on carbon.

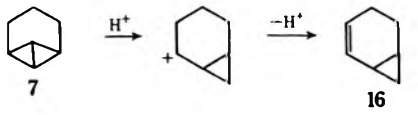
Bicyclobutane Derivatives 4 and 5.—Bicyclobutanes in general are very sensitive to acids and compounds **4** and **5** are not exceptions. As we noted previously,[3] some care is required to prevent acid-catalyzed rearrangement in the isolation and analysis of these compounds. However, it appeared that this propensity to rearrange could be used to advantage in elucidating the structures of **4** and **5**.

(10) This Grignard reagent presumably was a 55:45 mixture of the exo and endo isomers: (a) E. A. Hill, *J. Org. Chem.*, **31**, 20 (1966); (b) N. G. Krieghoff and D. O. Cowan, *J. Amer. Chem. Soc.*, **88**, 1322 (1966); (c) F. R. Jensen and K. L. Nakamaye, *ibid.*, **88**, 3437 (1966).

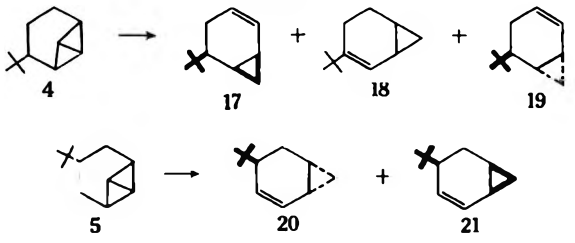
(11) J. E. Mulvaney and Z. G. Gardlund, *J. Org. Chem.*, **30**, 917 (1965).

(12) E. E. van Tamelen and R. J. Timmons, *J. Amer. Chem. Soc.*, **84**, 1067 (1962).

Compound **7** undergoes acid-catalyzed rearrangement to the vinylcyclopropane **16**.[4] In applying this reaction to the case at hand, we investigated a number of reagents to find conditions which would achieve reproducible results and found that magnesium bromide in ether led to the desired rearrangement but avoided the subsequent rearrangement of the primary products observed with more potent catalysts. Rearrangement of **4** and **5** proceeded cleanly; **4** gave three products, **17** (58%), **18** (38%), and **19** (4%), while **5** gave only two products, **20** (92%) and **21** (8%). The structures assigned to these products on the basis of arguments which follow are shown in Scheme I.



SCHEME I



The mass, nmr, ir, and uv data taken together establish that all of these products are *tert*-butyl derivatives of **16**. The fact that, as expected, one of the bicyclobutanes gives two products while the other gives three, one of which is the only trisubstituted olefin, is sufficient to distinguish between **4** and **5** and to establish that the trisubstituted olefin which must come from **4** must have structure **18**. Once the distinction between **4** and **5** has been made, the position, but not the stereochemistry, of the *tert*-butyl group in the other four products has also been made. Furthermore, the mass spectra of **20** and **21** clearly support the presence of an allylic *tert*-butyl group; both compounds give base peaks at *m/e* 93 (loss of *tert*-butyl), while in **17** and **19** the *m/e* 93 peaks are much weaker.

The stereochemical assignments can be deduced if one examines the conformational possibilities for the rearrangement products. It becomes apparent that the requirement of keeping the nonbonded interactions involving the *tert*-butyl group at a minimum causes the compounds to fall into the two conformational classes shown in Figure 1. Compounds in class A, which includes the parent compound **16** as well, have a pseudo chair conformation while compounds in class B have a pseudo boat conformation. In going from conformation A to conformation B, the plane of the three-membered ring is tilted toward the double bond causing the cyclopropyl proton designated as H_7 of the class B compounds to fall in the shielding region of the double bond. This effect is reflected in the nmr spectra. Each of the two compounds which fall in class B shows the signal from one proton shifted 0.3–0.4 ppm upfield from the highest field signals found in the spectra of the class A compounds.

It is also significant that compounds in class A have ultraviolet absorption maxima at somewhat longer

wavelengths than the maxima found for class B compounds. While the differences are small (4–5 nm), they support the idea of two conformational classes which differ in terms of the orientation of the three-membered ring with respect to the double bond.[13]

The distribution of rearranged products from **4** and **5** deserves some comment. If random bond breaking occurred, the product ratios would be **17**:**18**:**19** = 25:50:25 from **4** and **20**:**21** = 50:50 from **5**. The observed ratios of 58:38:4 and 92:8 are obviously far from random. Moreover, the trisubstituted olefin **18** is not the major product from **4** as one might expect if free cyclopropyl cations were intermediates. Inasmuch as both **4** and **5** must be locked in a conformation having the *tert*-butyl group equatorial, it is worth noting that the major products would be formed if a peripheral bond of the bicyclobutane ring were broken and a trans axial proton were lost.

Thus, it is possible that with the catalyst system we have employed, the main pathway for rearrangement involves transfer of a proton to a bond of the bicyclobutane, probably *via* a prior complex, followed by loss of a proton to an external base, as shown in Figure 2.[14] The reaction of the catalyst with **4** on the side away from the *tert*-butyl group would explain the preference for formation of **17**.

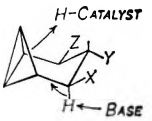


Figure 2.—Rearrangement of tricyclo[4.1.0.0^{2,7}]heptanes. **4** (X = Y = H, Z = *tert*-butyl) → **17**; **4** (X = *tert*-butyl, Y = Z = H) → **18**; **5** (X = Z = H, Y = *tert*-butyl) → **20**.

Experimental Section[15]

Hydrogenation of 2.—A solution of 20 mg of compound **2** in 10 ml of ethanol with 100 mg of 30% Pd/C absorbed 1 equiv of hydrogen within 2 hr at 25° (1 atm). After filtering, adding water, and extracting with pentane, glc (Carbowax 20M) showed a single peak which was collected to give 1-*tert*-butylnorbornane (**8**): ir 2960, 1395, 1370, 1330, 1310, 920 cm^{-1}; nmr (CCl_4) δ 0.92 (s, 9 H, *tert*-butyl), 1.0–1.8 (overlapping m, 10 H), 2.14 (broad s, 1 H, C-4); mass spectrum *m/e* (rel intensity) 152 (M^+, 10), 137 (56), 123 (61), 109 (27), 96 (41), 95 (58), 83 (19), 82 (13), 81 (100), 69 (17), 68 (21), 67 (38), 57 (74), 55 (42), 53 (15), 43 (19), 41 (67), 39 (22). *Anal.* Calcd for $C_{11}H_{20}$: C, 86.76; H, 13.24. Found: C, 86.62; H, 13.19.

***tert*-Butylcyclopentadiene.**—Sodium cyclopentadienide was prepared in liquid ammonia and alkylated with *tert*-butyl bromide following the method of Alder and Ache[5] to give a mixture of 1- and 2-*tert*-butylcyclopentadiene (10% yield): bp 53° (42 mm); [lit.[5] bp 33° (12 mm)]; ir (CCl_4) 3060, 2960, 1625, 1610, 1600 cm^{-1}; nmr (CCl_4) δ 1.17 and 1.19 (overlapping s, 9 H), 2.88 (m, 2 H), 5.8–6.65 (m, 3 H); mass spectrum, see Table I. Glc (2% SAIB at 80°) showed two partially resolved peaks in a ratio of 62:38.

1- and 2-*tert*-Butylnorbornene (9 and 10).—The mixture of 1- and 2-*tert*-butylcyclopentadiene (6 g) was heated with ethylene for 2.5 hr at 250° (175 atm). Glc analysis (XE-60, 120°) of the product (5.5 g) showed two peaks, t_r 1.00 and 1.30, in a ratio of 4:1 which were collected (XF-1150). The minor product was identified as 1-*tert*-butylnorbornene (**9**): ir (CCl_4) 3050, 2960, 1610, 1395, 1365, 1345 cm^{-1}; nmr (CCl_4) δ 0.97 (s, 9 H, *tert*-butyl) superimposed on 0.8–1.8 (m, 6 H), 2.80 (m, 1 H, C-4), 5.98 (apparent d, 2 H, C-2,3, probably center lines of AB q); mass spectrum, see Table I. *Anal.* Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.07. Found: C, 88.10; H, 12.04.

Hydrogenation of **9** over 30% palladium on carbon in ethanol at 25° (1 atm) gave a single product having a retention time (XF-1150) and ir spectrum identical with those of the sample of **8** derived from **2**.

The major product from the Diels–Alder reaction was identified as 2-*tert*-butylnorbornene (**10**): ir (CCl_4) 3050, 2960, 1615, 1395, 1365, 1325 cm^{-1}; nmr (CCl_4) δ 1.03 (s, 9 H, *tert*-butyl) superimposed on 0.9–1.8 (m, 6 H), 2.76 and 2.87 (overlapping multiplets, 2 H, C-1,4), 5.53 (broad d, 1 H, C-3); mass spectrum, see Table I. *Anal.* Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.07. Found: C, 87.82; H, 12.15.

2-*tert*-Butyl-2-hydroxynorbornane.—A solution of 5.1 g (0.047 mol) of norcamphor (Columbia Organic Chemicals Co.) in 5 ml of petroleum ether (bp 30–60°) was added dropwise to 0.047 mol of *tert*-butyllithium in 25 ml of pentane (Lithium Corp. of America) while cooling with an ice bath. The mixture was allowed to warm to room temperature (1 hr) and then was hydrolyzed. Extraction with pentane followed by distillation gave a forerun of norcamphor and 0.8 g of 2-*tert*-butyl-2-hydroxynorbornane (based on the method of synthesis, the *tert*-butyl group should be *exo*): bp 80° (1 mm); mp 63.5–64.5°; ir (CCl_4) 3610, 3500, 1395, 1365, 1310, 1160, 995 cm^{-1}; nmr (CCl_4) δ 0.92 (s, ~9 H, *tert*-butyl) superimposed on 0.8–2.4 (m); mass spectrum *m/e* (rel intensity) 168 (M^+, <0.1), 150 (0.1), 135 (3), 111 (100), 93 (29), 83 (84), 67 (62), 66 (20), 57 (60), 55 (47), 43 (54), 41 (56), 39 (22). *Anal.* Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.34; H, 11.82.

Treatment of this alcohol with hydrogen chloride under a variety of conditions including concentrated hydrochloric acid, hydrogen chloride in methanol–ether, and anhydrous hydrogen chloride in ether produced olefin **10** as the major product (identified on the basis of its glc retention times and infrared spectrum) along with complex mixtures of other materials which were not investigated. Under anhydrous conditions, a small amount of **9** may be formed.

Rearrangement of 2.—Compound **2** (100 mg) was stirred with 50 mg of aluminum chloride in 6 ml of ether at 25°. The isomerization of **2** was followed by glc analysis of aliquots. After 8 hr, the mixture was hydrolyzed and the products were extracted with pentane. Glc analysis (XF-1150, 50°) showed three peaks, t_r 0.90, 1.00, and 1.17, in ratios of 90:5:5 and a small amount of less volatile material (t_r 7.5, 9.0). The second peak was due to **2** and the first peak was identified as 2-*tert*-butylbicyclo[3.2.0]-hept-2-ene (**11**): ir (CCl_4) 3040, 2960, 1628, 1390, 1365 cm^{-1}; nmr[8] (CCl_4) δ 1.07 (s, 9 H, *tert*-butyl), 1.55–2.70 (5 H, endo C-4, C-6, C-7, complex multiplets centered at ~1.8, ~2 H, and 2.3, ~3 H), 2.89 (m ~ quintet, 1 H, C-5), 3.33 (m ~ t, 1 H, *exo*-C-4), 3.65 (m ~ t, 1 H, C-1), 5.41 (broadened t, J ~ 2 Hz, 1 H, C-3); mass spectrum, see Table I. *Anal.* Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 88.05; H, 12.09.

Hydrogenation of 3.—Inasmuch as **3** was very difficult to obtain free of **2**, a 1:1 mixture of **2** and **3** was hydrogenated over 30% Pd/C in ethanol at 25° (1 atm). Glc (XE-60, 98°) showed a 1:1 mixture of two peaks, t_r 0.88 and 1.00. The second peak was due to **8**. The more volatile compound was identified as *exo*-2-*tert*-butylnorbornane (**15**) by comparison of glc retention times (seven columns) and ir and mass spectra with those of the sample prepared from 2-chloronorbornane.

The following procedure is based on a method used for the preparation of hexamethylethane.[16] The Grignard reagent was prepared from 10.7 g (81 mmol) of *exo*-2-chloronorbornane[17] in ether. Then a solution of 1.36 g (7.4 mmol) of *tert*-butyl iodide and 6.77 g (73 mmol) of *tert*-butyl chloride was added followed by portionwise addition of 0.27 g of anhydrous cuprous chloride. Following hydrolytic work-up, fractional distillation gave 0.5 g of material, bp 59° (9.0 mm), that glc (XE-60, XF-1150) showed was mainly one compound which was collected and identified as **15**: ir (CCl_4) 2960, 1398, 1368 cm^{-1}; nmr, identical with that in the literature;[11] mass spectrum *m/e* (rel intensity) 152 (M^+, 0.2), 137 (2), 109 (3), 95 (100), 81 (12), 67 (26), 66 (14), 57 (35), 56 (58), 55 (12).

(13) It appears that interaction of the 1,7 bond with the p orbital at C-2 may be greater in the class A compounds.

(14) Although anhydrous conditions were employed, it is probable that a trace of water is necessary to effect rearrangement: W. R. Moore and N. L. Boardway, unpublished results.

(15) The general procedures given in footnote 31 of ref 3 were followed. Ultraviolet spectra were recorded with a Cary Model 14 spectrophotometer which was flushed with nitrogen employing oxygen-free isooctane as a solvent. Glc retention times are relative to the indicated peak (t_r = 1.00).

(16) R. C. Marker and T. S. Oakwood, *J. Amer. Chem. Soc.*, **60**, 2598 (1938).

(17) H. Kwart and R. K. Miller, *ibid.*, **78**, 5008 (1956).

p-Toluenesulfonylhydrazide (124 mg, 0.67 mmol) and 30 mg (0.20 mmol) of **10** in 1.5 ml of diglyme were heated in a bath at 160° for 18 hr. After cooling, adding water, and extracting with pentane, glc (XF-1150), showed a 1:2 mixture of **10** and its reduction product, *endo*-2-*tert*-butylnorbornane: ir (CCl_4) 2960, 1395, 1365 cm^{-1} (the fingerprint region is clearly different from that of **15**); nmr (CCl_4) δ 0.92 (s, 9 H, *tert*-butyl), 1.1–2.9 (m, 9 H), 2.22 (broad s, 2 H, C-1,4); mass spectrum *m/e* (rel intensity) 152 (M^+, 0.6), 137 (2.5), 109 (8), 95 (100), 81 (16), 67 (37), 66 (13), 57 (57), 56 (66), 55 (16). Hydrogenation of **10** in ethanol over 30% Pd/C gave the same compound. Less than 1% of **15** was found. Glc (XE-60, 96°) (t_r): **10** (1.00), **15** (1.36), *endo*-2-*tert*-butylnorbornane (1.55).

Rearrangement of 4.—A solution of magnesium bromide in ether was prepared by adding 1.80 g (9.6 mmol) of 1,2-dibromoethane in 25 ml of ether dropwise to 0.25 g (10 mmol) of magnesium in 75 ml of ether at reflux. The solution was filtered, sealed under nitrogen with a "No-Air" stopper, and stored at 5°. Compound **4** (200 μl) was added to 12 ml of the magnesium bromide solution. After 80 min at 25° glc showed that the starting material was absent. Water and pentane were added and the organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated by distillation of the solvent through a 26 × 1 cm Vigreux column. Glc analysis (XF-1150, 65°) showed three new peaks (t_r, **4** = 1.00): **17** (58%, 1.09), **18** (38%, 1.18), and **19** (4%, 1.44). The products were collected by glc (Carbowax 20M); spectral data are given below. Preliminary reactions established that the product ratios did not change with time. Aluminum chloride, stannic chloride, and mercuric chloride, all in ether, quickly led to complex mixtures as a consequence of subsequent rearrangement of the initial products.

endo-**5**-*tert*-**Butylbicyclo[4.1.0]hept-2-ene** (**17**).—Spectral data: ir (CCl_4) 3060, 3030, 2960, 1635, 1390, 1365, 1025 cm^{-1}; uv λ_{max} (ethanol) 198 ± 1 nm (ϵ 5200); nmr (CCl_4) δ 0.05–0.27 (m, 1 H, endo C-7), 0.98 (s, 9 H, *tert*-butyl) superimposed on 0.75–1.50 (m, 4 H), 1.75–2.03 (m, 2 H, C-4), 5.55 (d of t, 1 H, C-3), 5.85 (br d, 1 H, C-2); mass spectrum *m/e* (rel intensity) 150 (M^+, 2), 135 (5), 107 (7), 94 (22), 93 (20), 91 (19), 83 (18), 80 (19), 79 (49), 78 (15), 77 (20), 57 (100), 55 (15). *Anal.* Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 88.07; H, 12.11.

3-*tert*-**Butylbicyclo[4.1.0]hept-2-ene** (**18**).—Spectral data: ir (CCl_4) 3065, 3050, 3000, 2960, 1640, 1390, 1365 (d), 1020 cm^{-1}; uv λ_{max} (ethanol) 204 ± 1 nm (ϵ 4300); nmr (CCl_4) δ 0.35 to ~0.8 (m, ~2 H, C-7), 0.98 (s, 9 H, *tert*-butyl) superimposed on ~1.0–1.4 (m, ~2 H), 1.4–2.15 (m, 4 H), 5.72 (m, 1 H, C-2); mass spectrum *m/e* (rel intensity) 150 (M^+, 21), 135 (50), 107 (54), 94 (35), 93 (48), 91 (31), 79 (48), 77 (26), 57 (100), 55 (22). *Anal.* Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.95; H, 12.13.

exo-**5**-*tert*-**Butylbicyclo[4.1.0]hept-2-ene** (**19**).—Spectral data: ir (CCl_4) 3065, 3035, 3000, 2960, 1645, 1395, 1365, 1025 cm^{-1}; uv λ_{max} (ethanol) 202 ± 1 nm (ϵ 4800); nmr (CCl_4) δ 0.30 to ~0.9 (m, 2 H, C-7), 0.97 (s, 9 H, *tert*-butyl) superimposed on ~1.0–2.1 (m, 5 H), 5.30 (m, 1 H), 5.90 (m, 1 H); mass spectrum *m/e* (rel intensity) 150 (M^+, 6), 135 (6), 107 (8), 94 (16), 93 (22), 91 (15), 79 (26), 77 (15), 57 (100).

Rearrangement of 5.—Compound **5** (120 μl) was added to 15 ml of 0.1 *M* magnesium bromide in ether. After 4 days at 25°, the mixture was worked up as above. Glc (XF-1150, 65°) showed the absence of **5** and two new peaks (t_r, **5** = 1.00), **20** (92%, 1.06) and **21** (8%, 1.26), which were collected; spectral data are given below. The same ratios were observed at shorter times when the rearrangment was incomplete.

exo-**4**-*tert*-**Butylbicyclo[4.1.0]hept-2-ene** (**20**).—Spectral data: ir (CCl_4) 3060, 3030, 2995, 2960, 1630, 1395, 1365, 1020 cm^{-1}; uv λ_{max} (ethanol) 198 ± 1 nm (ϵ 4800); nmr (CCl_4) δ −0.15 to +0.05 (m, 1 H, endo C-7) 0.83 (s, 9 H, *tert*-butyl) superimposed on ~0.8–1.3 (m, 4 H), 1.6–2.4 (m, 2 H), 5.60 and 5.90 (two d, part of AB q centered at 5.75, 2 H, C-2,3); mass spectrum *m/e* (rel intensity) 152 (M^+, 2) 135 (1), 107 (4), 94 (20), 93 (100), 92 (16), 91 (25), 79 (19), 77 (27), 57 (68). *Anal.* Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 88.12; H, 12.21.

endo-**4**-*tert*-**Butylbicyclo[4.1.0]hept-2-ene** (**21**).—Spectral data: ir 3065, 3030, 3000, 2960, 1635, 1395, 1365, 1020, cm^{-1}; uv λ_{max} (ethanol) 203 ± 1 nm (ϵ 5600); nmr (CCl_4) δ 0.4–0.8 (m, 2 H, C-7), 0.85 (s, 9 H, *tert*-butyl) superimposed on 0.9–2.2 (m, 5 H), ~5.3 (m, 1 H), ~5.9 (m, 1 H); mass spectrum *m/e* (rel intensity) 150 (M^+, 1), 135 (2), 107 (2), 94 (16), 93 (100), 92 (11), 91 (26), 79 (22), 77 (29), 57 (93).

Registry No.—**2**, 29339-27-3; **3**, 29339-28-4; **4**, 29339-29-5; **5**, 29339-30-8; **8**, 29339-31-9; **9**, 29339-32-0; **10**, 29339-33-1; **11**, 29339-34-2; **15**, 1125-54-8; **17**, 29339-36-4; **18**, 29339-37-5; **19**, 29339-38-6; **20**, 29339-39-7; **21**, 29339-40-0; 2-*tert*-butyl-2-hydroxynorbornane, 29339-41-1.

Palladium(II)-Catalyzed Aromatic Substitution[1]

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Pd(II) salts in the presence of nucleophiles (X^-) oxidize aromatics or mercurated aromatics to coupled aromatics. With phenylmercury salts the reaction is $2PhHg^+ + Pd^{II} + X^- \rightarrow Ph_2 + Pd^0 + 2Hg^{2+} + X^-$. However, if certain oxidants are added to the reaction mixture, the course of the reaction changes to give substituted aromatics: $PhHg^+ + Pd^{II} + X^- (+ Ox.) \rightarrow PhX + Hg^{2+} + Pd^{II}$. Examples of the reaction were obtained for OAc^-, N_3^-, Cl^-, NO_2^-, Br^-, CN^-, and SCN^- as nucleophiles; Cr(VI), $Pb(OAc)_4$, $NaClO_3$, $KMnO_4$, $NaNO_3$, and $NaNO_2$ as oxidants; and benzene, toluene, phenyl acetate, and mercurated benzene and toluene as aromatic substates. Acetic acid was generally used as solvent, but in some cases acetonitrile and nitrobenzene were used. The reaction gives a substitution pattern characteristic of an electrophilic substitution reaction. The reaction most likely proceeds either *via* a Pd(II) aryl or by generation of a Pd(IV) species by the oxidant, followed by attack of the Pd(IV) species on the aromatic substrate.

Although direct hydroxylations or acetoxylations of benzenoid compounds do not occur readily,[2] several metal ion catalyzed direct substitution reactions involving Fe(II)[3] and Pb(IV)[4-6] have recently been reported. This paper will describe a Pd(II)-catalyzed direct aromatic substitution not only of acetate but of other groups as well.

The possibility that Pd(II) will catalyze the oxidation of aromatic compounds by inorganic oxidants is suggested by our previous work on the Pd(II)-catalyzed oxidation of olefins in the presence of such oxidants. It has been previously reported[7] that Cu(II) changes the nature of olefin oxidations by Pd(II). Thus, in

(1) Hercules Research Center Contribution No. 1538.

(2) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, Amsterdam, 1965.

(3) G. A. Hamilton, R. J. Workman, and L. Woo, *J. Amer. Chem. Soc.*, **86**, 3390 (1964).

(4) D. R. Harvey and R. O. C. Norman, *J. Chem. Soc.*, 4860 (1964).

(5) R. E. Partch, *J. Amer. Chem. Soc.*, **89**, 3662 (1967).

(6) E. C. Taylor, H. W. Altland, R. H. Danforth, G. McGillivray, and A. McKillop, *ibid.*, **92**, 3520 (1970).

(7) P. M. Henry, *J. Org. Chem.*, **32**, 2575 (1967).

TABLE I

OXIDATION OF BENZENE OR PHENYLMERCURIC ACETATE BY A COMBINATION OF $Pd(OAc)_2$ AND $K_2Cr_2O_7$ IN ACETIC ACID AT 90° [a]

Expt no.	$Pd(OAc)_2$, mmol	$K_2Cr_2O_7$, mmol	Aromatic, (mmol)	Other reagents (mmol)	Time, hr	Phenyl acetate, mmol	Biphenyl, mmol
1	1.0	15	PhHgOAc (10)	LiOAc (25)	24	0.5	0.06
2	1.0	15	Benzene (10)	LiOAc (25)	23	1.45	<0.015
3	None	15	Benzene (10)	LiOAc (25)	23	<0.01	<0.02
4	1.0	None	PhHgOAc (10)	LiOAc (25)	23	<0.05	0.95
5	0.5	15	Benzene (33)	CH_3SO_3H (3)	16	2.03	<0.015
6	1.0	15	Benzene (55)	$Hg(OAc)_2$ (3)	20	1.35	<0.02
7	1.0	15	Benzene (55)	$Hg(OAc)_2$ (3)	40	1.35	<0.02

[a] All contain 25 ml of acetic acid.

the absence of Cu(II), Pd(II) in acetic acid oxidizes ethylene to vinyl acetate.

$$C_2H_4 + Pd^{II} + 2OAc^- \xrightarrow{HOAc} C_2H_3OAc + Pd^0 + HOAc \quad (1)$$

However, if Cu(II) is added 1,2-disubstituted ethanes are also formed (X = OAc or Cl).

$$C_2H_4 + 2CuX_2 + OAc^- \xrightarrow[HOAc]{PdCl_2} XCH_2CH_2OAc + 2CuX + X^- \quad (2)$$

The most reasonable mechanism for the result[7] is that the reactions producing vinyl acetate and saturated esters proceed through a common acetoxypalladation adduct, 1, and Cu(II) is capable of changing the mode

$$\text{-PdOAc} + C_2H_4 \longrightarrow \text{-PdCH}_2\text{CH}_2\text{OAc} \;(1) \begin{cases} \longrightarrow \text{-PdH} + CH_2{=}CHOAc \\ \xrightarrow{CuX_2} \text{-PdX} + XCH_2CHOAc \end{cases} \quad (3)$$

of decomposition of the intermediate. It has been demonstrated that NO_3^- [8] as well as other oxidants[9] can be used in place of Cu(II).

If oxidants can cause Pd(II) alkyls to decompose with substitution, it seems possible that Pd(II) aryls can also be made to decompose with substitution. Pd(II) aryls have been postulated to be intermediates in several Pd(II)-catalyzed reactions such as carbonylation,[10] olefin arylation,[11] and oxidative coupling.[12,13] This work was undertaken to test this hypothesis.

Under certain conditions, $Pd(OAc)_2$ is reported to give phenyl acetate.[14] However, this reaction is inhibited by oxygen and apparently has radical character.

One specific example of the general reaction described in this paper, the Pd(II)-catalyzed nitration of benzene, has previously been reported.[15] However, the necessity for an oxidant in order for the reaction to proceed was apparently not recognized.

Results

In the initial work, $K_2Cr_2O_7$ was used as the oxidant. As the results in Table I show, this oxidant in the presence of $Pd(OAc)_2$ will indeed give phenyl acetate. Control experiments showed that, in the absence of $K_2Cr_2O_7$, as expected, only biphenyl is produced (expt 4); in the absence of $Pd(OAc)_2$ (expt 3), neither is formed. Note that the addition of oxidant actually inhibits the formation of biphenyl (compare expt 1 and 4). The benzene was initially introduced as phenylmercuric acetate, but it was later found that benzene itself worked as well. Addition of $Hg(OAc)_2$ did not improve the yield (expt 2 and 6). Neither did running the reaction for longer periods of time (expt 6 and 7). Control experiments indicated phenyl acetate gradually disappeared under the reaction conditions. The reaction was definitely catalytic in Pd(II). In expt 5, 4 mol of product per mole of Pd(II) was formed. The reaction mixtures of Table I were heterogeneous because of limited solubility of the metal salts.

A number of oxidants other than $K_2Cr_2O_7$ were tested on benzene. Results are listed in Table II.

TABLE II

TEST OF VARIOUS OXIDANTS FOR PHENYL ACETATE PRODUCTION FROM BENZENE[a]

$Pd(OAc)_2$, mmol	Oxidant	Phenyl acetate, mmol
1.0	$Tl(OAc)_3$	<0.01
1.0	$Pb(OAc)_4$	0.51
...	$Pb(OAc)_4$	<0.01
1.0	MnO_2	<0.01
1.0	$KMnO_4$	0.27
...	$KMnO_4$	<0.01
1.0	CrO_3	0.25
...	CrO_3	<0.01
1.0	V_2O_5	<0.01
1.0	Pb_3O_4	<0.01
1.0	$NaNO_3$[b]	0.14
...	$NaNO_3$	<0.01
1.0	$NaNO_2$[b]	0.08
...	$NaNO_2$	<0.01
1.0	$CuCl_2$	<0.01
1.0	$NaClO_3$[c]	0.09
...	$NaClO_3$	<0.01

[a] All reaction mixtures contain 25 ml of acetic acid, 10 mmol of the oxidant, 33 mmol of benzenes, and 3 mmol of CH_3SO_3H. Run 20 hr at 90°. [b] Nitrobenzene (*ca.* 0.1 mmol) also present. [c] Chlorobenzene (1.65 mmol) also present.

$Pb(OAc)_4$, $KMnO_4$, CrO_3, $NaNO_3$, and $NaClO_3$ gave at least some phenyl acetate while the others gave no detectable amount. Some, such as Pb_3O_4, may have failed owing to insolubility in the reaction medium. If Pd(II) plus oxidant gave the reaction, controls were run to show that the oxidant itself did not oxidize benzene to phenyl acetate. When $NaNO_3$ and $NaNO_2$

(8) M. Tamura and T. Yasui, *Chem. Commun.*, 1209 (1968).
(9) P. M. Henry, unpublished results.
(10) P. M. Henry, *Tetrahedron Lett.*, 2285 (1968).
(11) R. F. Heck, *J. Amer. Chem. Soc.*, **90**, 5518 (1968), and following papers.
(12) J. M. Davidson and C. Triggs, *J. Chem. Soc. A*, 1324 (1968).
(13) M. O. Unger and R. A. Fouty, *J. Org. Chem.*, **34**, 18 (1969).
(14) J. M. Davidson and C. Triggs, *J. Chem. Soc. A*, 1331 (1968).
(15) T. Tisue and W. J. Downs, *Chem. Commun.*, 410 (1969).

TABLE III

SUBSTITUTION OF AROMATICS WITH NUCLEOPHILES OTHER THAN ACETATE[a]

Salt (mmol)	Nucleophile (mmol)	Aromatic (mmol)	Oxidant (mmol)	Solvent[b]	Products (mmol)
$Pd(OAc)_2$ (1.0)	LiCl (25)	PhHgOAc (10)	$K_2Cr_2O_7$ (15)	HOAc	PhCl (1.56)[c]
	LiCl (25)	PhHgOAc (10)	$K_2Cr_2O_7$ (15)	HOAc	PhCl (0.17)[c]
$Pd(OAc)_2$ (1.0)	LiBr (25)	PhHgOAc (10)	$K_2Cr_2O_7$ (15)	HOAc	PhBr (1.2)[c]
	LiBr (25)	PhHgOAc (10)	$K_2Cr_2O_7$ (15)	HOAc	PhBr (1.07)[c]
$Pd(OAc)_2$ (1.0)	LiF (25)	PhHgOAc (10)	$K_2Cr_2O_7$ (15)	HOAc	PhOAc (0.33), PhF (<0.02)
$Pd(OAc)_2$ (1.0)	LiN_3 (25)	PhHgOAc (10)	$K_2Cr_2O_7$ (15)	HOAc	PhOAc (0.19), PhN_3 (0.4)
	LiN_3 (25)	PhHgOAc (10)	$K_2Cr_2O_7$ (15)	HOAc	PhN_3 (0.2)
$Pd(OAc)_2$ (1.0)	LiN_3 (25)	PhHgOAc (10)	$Pb(OAc)_4$ (10)	HOAc	PhOAc (0.13), PhN_3 (0.77)
	LiN_3 (25)	PhHgOAc (10)	$Pb(OAc)_4$ (10)	HOAc	PhOAc (0.13), PhN_3 (0.015)
$Pd(OAc)_2$ (1.0)	NaSCN (10)	PhHgOAc (10)	$Pb(OAc)_4$ (10)	CH_3CN	PhOAc (4.75), PhSCN (0.94), Ph_2 (2.66)
$Pd(OAc)_2$ (1.0)	NaCNO (43)	PhHgOAc (10)	$Pb(OAc)_4$ (10)	CH_3CN	PhNCO (<0.01)
$Pd(OAc)_2$ (1.0)	NaCN (50)	PhHgOAc (10)	$Pb(OAc)_4$ (10)	CH_3CN	PhCN (0.18)[c]
$Pd(OAc)_2$ (1.0)		PhOAc (10)	$NaClO_3$ (10)	HOAc	Chlorophenyl acetate (0.79), 47% ortho, 47% para, 6% meta
$K_2Pd_2Cl_6$ (5)		PhHgOAc (5)		HOAc	PhOAc (0.14),[d] PhCl (1.55)

[a] Reaction condition 90° for 18–22 hr when HOAc is solvent. Temperature was 75° when CH_3CN was solvent. [b] 25 ml of solvent used for all runs but the last run for which 10 ml was used. [c] <0.01 mmol of PhOAc present. [d] Some dichlorobenzenes also present.

TABLE IV

PREPARATION OF CRESOL ACETATES BY OXIDATION OF TOLUENE BY $Pd(OAc)_2$, $K_2Cr_2O_7$ IN ACETIC ACID[a]

$Pd(OAc)_2$, mmol	Aromatic (mmol)	Other reagents (mmol)	Reaction conditions	Cresol acetate, mmol	Distribution, % Ortho	Meta	Para
0.5	Toluene (32)	$3CH_3SO_3H$ (3.1)	16 hr at 90°	1.0[b]	19	62	19
0.5	Toluene (32)	$Hg(OAc)_2$ (3)	16 hr at 90°	1.95[c,d]	12	39	49
1.0	*p*-TolylHgOAc (20)	LiOAc (25)	16 hr at 90°	0.4[d]	0	0	100
0.5	Toluene (32)	CH_3SO_3H (3.1)	19 hr at 50°	0.082[d]	5	19	76
0.5	Toluene (32)	$Hg(OAc)_2$ (3)	22 hr at 50°	0.16[d]	6	19	75

[a] $K_2Cr_2O_7$ (15 mmol) and acetic acid (25 ml) used. [b] Benzyl acetate (0.03 mmol) also formed. [c] Bitolyl (0.23 mmol) also formed; mainly 3,3, 3,4, and 4,4. [d] No benzyl acetate detected. Limit of detection 1% of total acetate product.

were used as oxidants, a second product, nitrobenzene, was formed and $NaClO_3$ gave chlorobenzene. This result suggested other nucleophiles than acetate could be substituted on the aromatic ring. Table III gives the results of experiments using other nucleophiles. LiCl, LiBr, LiN_3, NaSCN, and NaCN gave substitution while LiF and NaCNO did not. The failure of NaCNO could be due to solubility. LiBr and LiN_3 also gave substitution in the absence of Pd(II) with $K_2Cr_2O_7$ as the oxidant; so in these cases substitution was most likely not Pd(II)-catalyzed but results from oxidation of the Br^- or N_3^- to radicals or cations. However, when $Pb(OAc)_4$ was used as oxidant with LiN_3, only traces of phenyl azide were formed in the absence of Pd(II).

A limited number of aromatics were tested for the substitution reaction. As shown in Table III, phenyl acetate did give chlorophenyl acetates in an isomer ratio characteristic of an electrophilic substitution. Attempts to produce diacetoxybenzenes from phenyl acetate met with little success because the phenyl acetate was consumed in side reactions. Only traces of diacetoxybenzenes, mainly hydroquinone diacetate, were formed. When equal amounts of benzene and nitrobenzene were oxidized in acetic acid, less than 0.01 mmol of nitrophenyl acetate was formed although 1.43 mmol of phenyl acetate was present.

The results of several experiments aimed at producing cresol acetates from toluene are given in Table IV. At 90°, $Pd(OAc)_2$ gave a distribution with high amount of meta isomer. Little, if any, benzyl acetate was formed in these reactions. Addition of $Hg(OAc)_2$, however, increased the *p*-cresol acetate ratio as well as the conversion. Lowering the temperature also increased the para isomer, and, if pure *p*-tolylmercuric acetate was used as aromatic, only *p*-cresol acetate was formed.

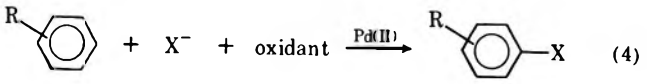
Acetic acid was generally used as solvent because most of the inorganic salts were at least partially soluble in this solvent. Acetonitrile was not quite so effective as acetic acid when $K_2Cr_2O_7$ was the oxidant but was better than acetic acid when $Pb(OAc)_4$ was the oxidant. Dimethylformamide and nitrobenzene gave little or no reaction.

Finally, Table V gives the results of a study of possible replacements for Pd(II). All the metal salts

gave less than 10% of the conversion to phenyl acetate obtained with $PdCl_2$ under comparable reaction conditions.

Discussion

The present work describes a new quite general aromatic substitution reaction (eq 4). Substitution

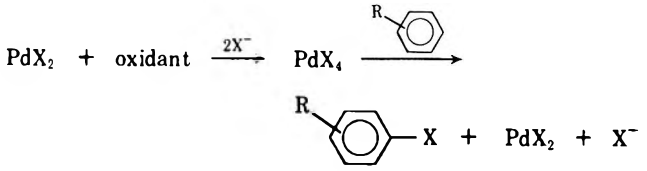


products have been obtained for $X^- = OAc^-$, N_3^-, Cl^-, NO_2^-, CN^-, and SCN^- and for $K_2Cr_2O_7$, $Pb(OAc)_4$, $KMnO_4$, $NaClO_3$, $NaNO_3$, and $NaNO_2$ as oxidants. Benzene, toluene, phenyl acetate, and mercurated benzene and toluene have been used as aromatic reactants. Other combinations of oxidants, nucleophiles, and aromatics very likely will give the reaction, especially if nonhydroxylic solvents which will dissolve all the reagents can be found. Because of its solubility in organic solvents $Pb(OAc)_4$ appears to be the most generally useful oxidant. Of course $Pd(OAc)_4$ itself will acetoxylate activated aromatics such as anisole but not benzene or toluene.[4] Control experiments (see Table II) indicated that no acetoxylation of benzene occurred in the absence of Pd(II).

Unfortunately, the usefulness of the reaction is limited by slow rates, side reactions, and the need for expensive oxidizing agents. However, it could be the preferred means of producing substituted aromatics which are not readily available by other means. This is especially true if the substituted aromatic formed in the reaction is deactivated so it will not undergo that further reaction.

The present work does not permit the proposal of a definite mechanism but some observation concerning mechanisms can be made. It does not appear related to the radical-type acetoxylations by $Pd(OAc)_2$ alone[14] since the present reaction gave cresol acetates with toluene while benzyl acetates were obtained in the radical reaction. Except for Br^- and N_3^- with $K_2Cr_2O_7$, the reaction cannot proceed by oxidation of X^- to reactive $X\cdot$ or X^+ species since control experiments demonstrated that in the other cases Pd(II) is required. The reaction gives substitution patterns consistent with an electrophilic substitution. The lack of reactivity of nitrobenzene is also consistent with an electrophilic reaction.

One of the two most likely mechanisms for the reaction appear to be (1) oxidation of Pd(II) to Pd(IV) followed by attack of the Pd(IV) on the aromatic.



Support for this scheme comes from the fact that Pd(IV) will oxidize aromatics to the observed products. Also HNO_3 is reported to oxidize Pd(II) to Pd(IV) salts.[16] Furthermore, $CuCl_2$ which causes Pd(II) alkyls to decompose does not give the aromatic substitution. The reason for this could be that $CuCl_2$ is not a vigorous enough oxidizing agent to convert Pd(II) to Pd(IV). Thus the oxidation potential of $PdCl_6^{2-}$ in aqueous solution has been estimated to be about 1.20 V[17] while that for $CuCl_2$ is only about 0.54 V.[18] On the other hand, the successful oxidants in Table II have potentials in aqueous systems which are close to those of $PdCl_6^{2-}$. Of course there is considerable uncertainty as to the actual potentials in the reaction systems.

(16) C. C. Addison and B. G. Ward, *Chem. Commun.*, 155 (1966).

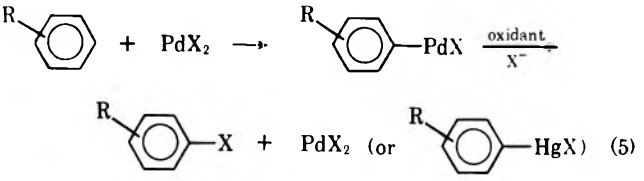
TABLE V

SUBSTITUTES FOR Pd(II) IN THE AROMATIC SUBSTITUTION REACTION[a]

Metal salt	PhOAc (mmol)	Metal salt	PhOAc (mmol)
$PtCl_2$	0.098	$OsCl_3$	0.072
$RhCl_3$	0.010	$IrCl_3$	<0.005
$RuCl_3$	0.11	AgOAc	0.026

[a] All reaction mixtures contain 15 mmol of $K_2Cr_2O_7$, 25 mmol of PhHgOAc, 25 mmol of LiOAc, and 25 ml of HOAc. Most reaction mixtures contained some biphenyl product.

The second mechanism is (2) formation of a Pd(II) aryl by direct substitution or exchange with a Hg(II) aryl. The Pd(II) aryl is decomposed by the oxidant to give substitution products (eq 5). The role of the



oxidant in this mechanism is uncertain but it must somehow participate in the decomposition step since control experiments demonstrate that X^- will not attack the Pd(II) aryl in the absence of oxidant. Rather the Pd(II) aryl decomposes to biphenyl. The oxidant most likely causes decomposition by removal of electrons from the Pd(II) simultaneous with attack of X^- on the Pd(II)–carbon bond. As discussed in the introduction, this mechanism is consistent with that previously proposed for decomposition of Pd(II) alkyls for which there is evidence that Pd(IV) species are not involved.[9]

The fact that $CuCl_2$ does not give the aromatic substitution reaction does not rule out mechanism 2 since it is quite reasonable that Pd(II) aryls are more stable than Pd(II) alkyls and require stronger oxidants to decompose them. The almost complete elimination of biphenyl as a product (compare expt 1 and 4 in Table I) would not be predicted by the first mechanism unless all the Pd(II) had been converted to Pd(IV). This result is expected, however; the Pd(II) aryl is intercepted by the oxidant before it can decompose to biphenyl.

Experimental Section

Reagents.—Palladium(II) chloride was purchased from Engelhardt Industries, Inc. The thallic acetate was prepared as described earlier.[19] Hydroquinone diacetate was prepared by

(17) W. M. Latimer, "Oxidation Potentials," 2nd ed, Prentice-Hall, Englewood Cliffs, N. J., 1952 p 203.

(18) Reference 17, p 186.

(19) P. M. Henry, *J. Amer. Chem. Soc.*, **88**, 1597 (1966).

acetylating hydroquinone. The tetraacetate was purchased from K & K Laboratories, Inc.

Analyses.—All analyses were by vapor phase chromatography (vpc). Before analysis, all runs using acetic acid as solvent were diluted with CH_2Cl_2, and the organic phase was washed several times with water, dried, and concentrated to a known volume. Runs using other solvents were usually injected directly. Most reaction mixtures were analyzed using a 6-ft column packed with 20% Carbowax 20M on an 70–80 mesh ABS support. The temperature was programmed from 80 to 200° at a rate of 7.5°/min. The helium flow rate was 60 ml/min. Biphenyl analyses were carried out using a 6-ft Apiezon N on ABS, 15% 90–100 mesh. The temperature was 210° and the flow rate was 60 ml/min. Bitolyl analyses were carried out on the same column at 230°. Cresol acetate analyses were carried out using a 12 ft × $^3/_{16}$ in diisodecyl phthalate, tri-*p*-tolyl phosphate trimer acid on G as Chrom 2, 5 g/95 g at 140°. The flow rate was 60 ml/min. The benzyl acetate and *m*-cresol acetate were not resolved on this column and the capacity was too low to allow this peak to be collected for nmr. However, the per cent of benzyl acetate compared to total acetate product was determined by the nmr of the reaction mixture. In the phenyl acetate oxidation both the phenyl acetate and diacetoxybenzenes were analyzed using the 6-ft Apiezon N programmed from 150 to 250° at 7.5°/min; the flow rate was 60 ml/min. These same conditions were used for phenyl isothiocyanate and benzonitrile analyses.

Identification of Products.—The phenyl acetate, phenyl azide, nitrobenzene were identified by vpc retention time as well as by collection from the vpc eluent followed by infrared in a microcell. The chlorobenzene was identified by vpc retention time and mass spectrometer analysis. The infrared spectrum of the phenyl isothiocyanate reaction mixture indicated this product was present. This was further confirmed by vpc retention time. Benzonitrile was identified by vpc retention time alone since there was not enough material for collection. The absence of phenyl isocyanate was demonstrated by adding ethanol to the reaction mixture followed by analysis for phenylurethane using the 6-ft Apiezon N at 230°. Fortification with an authentic sample demonstrated that none was present.

Registry No.—Benzene, 71-43-2; phenylmercuric acetate, 62-38-4; toluene, 108-88-3; $Pd(OAc)_2$, 3375-31-3; $K_2Cr_2O_7$, 7778-50-9.

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Oxidation of Organic Compounds with Cerium(IV). XII. Oxidative Cleavage and Ketone Formation of Alkylphenylcarbinols[1]

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Products from the oxidation of methyl-, ethyl-, isopropyl-, and *tert*-butylphenylcarbinols by 2 equiv of ceric ammonium nitrate in 50% aqueous acetonitrile at 90° are reported. The relative rates of oxidative cleavage to formation of the corresponding carbonyl compound are given by the ratios of benzaldehyde to alkyl phenyl ketone that were obtained from the alkylphenylcarbinols. These ratios are 0.04, 3.30, 184, and 195 for the methyl-, ethyl-, isopropyl-, and *tert*-butylphenylcarbinols, respectively. Previously reported results indicate that the cerium(IV) oxidative cleavage of alcohols is a one-electron oxidation, and the present results suggest that oxidative cleavage of an alcohol by cerium(IV) will occur if a radical as stable as a secondary carbon radical is produced by cleavage. The corresponding alkyl nitrates are the main products obtained from the ethyl and isopropyl radicals, but no *tert*-butyl nitrate from the *tert*-butyl radical is reported. It is proposed that the *tert*-butyl radical is oxidized to isobutylene.

Oxidations of alcohols by cerium(IV) tend to be oxidative cleavages, not reactions that form the corresponding carbonyl compounds.[1a,2] For example, none of the corresponding ketones were obtained from the cerium(IV) oxidation of 1,2-diarylethanols,[1a,3] *exo*- and *endo*-bicyclo[2.2.1]heptan-2-ol,[2] or bicyclo[2.2.2]-octan-2-ol.[2] These oxidative cleavages have been shown to be one-electron oxidations which involve the formation of an intermediate radical.[1a,2,3] Moreover,

$$R_3COH + Ce^{IV} \longrightarrow R_2C{=}O + Ce^{III} + R\cdot$$

$$R\cdot + Ce^{IV} \longrightarrow Ce^{III} + \text{products from } R^+$$

it has been shown that the rate of cleavage is dependent on the stability of the radical, and, in the transition state that leads to cleavage, a fair amount of positive charge develops on the fragment which becomes the radical.[1a,3]

In two cases, benzyl alcohols[4] and cyclopropanemethanol,[5] the alcohol is oxidized to the corresponding aldehyde by cerium(IV). In both of these cases, the carbon radicals which would have to be formed during the cleavage reaction, substituted phenyl and cyclopropyl radicals, are relatively unstable. Evidently, when the radical which must be formed is unstable enough, another process takes over which leads to the corresponding carbonyl compound. In order to better define the stability of the radical needed for cleavage to occur, we studied a series of alkylphenylcarbinols in which the alkyl groups were methyl, ethyl, isopropyl, and *tert*-butyl with particular attention being paid to the relative rates of cleavage to ketone formation. This paper reports the results of this study.

Results

Methyl-, ethyl-, isopropyl-, and *tert*-butylphenylcarbinols were oxidized by 2 equiv of ceric ammonium nitrate (CAN) in 50% aqueous acetonitrile at 90°. The oxidations took 1.5–6 min. The absolute yields of the recovered starting material and products were

(1) (a) Part XI: P. M. Nave and W. S. Trahanovsky, *J. Amer. Chem. Soc.*, in press. (b) This work was partially supported by Public Health Service Grant GM 13799 from the National Institute of General Medical Sciences and Grant GP-18031 from the National Science Foundation. We thank these organizations for their support. (c) Alfred P. Sloan Research Fellow, 1970–1972. (d) Preliminary communication: Abstracts of the Joint Chemical Institute of Canada–American Chemical Society Conference, Toronto, May 1970, PHYS 31.

(2) W. S. Trahanovsky, P. J. Flash, and L. M. Smith, *J. Amer. Chem. Soc.*, **91**, 5068 (1969).

(3) P. M. Nave and W. S. Trahanovsky, *ibid.*, **90**, 4755 (1968).

(4) (a) W. S. Trahanovsky and L. B. Young, *J. Chem. Soc.*, 5777 (1965); (b) W. S. Trahanovsky, L. R. Young, and G. L. Brown, *J. Org. Chem.*, **32**, 3865 (1967).

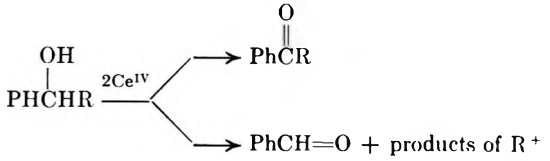
(5) L. B. Young and W. S. Trahanovsky, *ibid.*, **32**, 2349 (1967).

TABLE I
ABSOLUTE YIELDS OF RECOVERED STARTING MATERIAL AND PRODUCTS FROM THE CERIC AMMONIUM NITRATE OXIDATION OF ALKYLPHENYLCARBINOLS, PhCHOHR[a]

	Yield, %						
R	PhCHOHR	PhCOR	PhCHO	$RONO_2$[b]	ROH[b]	$RNHCOCH_3$	Yield of PhCHO/ yield of PhCOR
$-CH_3$[c]	26.2	55.2 ± 0.2	2.83 ± 0.08				0.04[d]
$-CH_2CH_3$[e]	18.2 ± 1.3	18.2 ± 0.5	60.0 ± 1.0	36 (60[f])			3.30 ± 0.04
$-CH(CH_3)_2$[g]	3.40 ± 0.06	0.51 ± 0.04	91.9 ± 1.3	64 (70[f])		2.0 ± 0.3	184 ± 13[h]
$-C(CH_3)_3$[e]	<0.5	0.49 ± 0.03	94.9 ± 1.2	0	13.8 (14.5[f])	11.2 ± 0.4	195 ± 23[i]

[a] In 50% aqueous acetonitrile at 90°, 1.5–6 min, 0.5 *M* CAN and 0.25 *M* alcohol initially; yields were determined by glpc unless otherwise noted. [b] Yields were determined by nmr. [c] Based on two runs. [d] This number was calculated by assuming that the ketone had been partially oxidized. [e] Based on four runs. [f] Yield was based on the amount of cleavage. [g] Based on three runs. [h] Based on six runs. [i] Based on seven runs.

determined by glpc and nmr analysis using internal standards. These yields are reported in Table I. From the ratios of benzaldehyde to ketone that were obtained from the alkylphenylcarbinols it is seen that ketone formation is the main pathway for methylphenylcarbinol, but oxidative cleavage is the almost



exclusive route for isopropyl- and *tert*-butylphenylcarbinols. Both pathways are important for ethylphenylcarbinol. The material balance is high, >95%, in all cases except for methylphenylcarbinol where it is 84%. In this case, the oxidation of acetophenone to products that are not recovered by our work-up procedure (*i.e.*, acidic products) most likely competes with the oxidation of methylphenylcarbinol. This assumption is substantiated by the fact that the oxidation of methylphenylcarbinol with 1 equiv of CAN gave rise to a 4:5 ratio of ketone to alcohol, whereas, under the normal conditions of 2 equiv of CAN, a 2:1 ratio of ketone to starting material was obtained.

The detection and identification of the products arising from the aliphatic moiety in the cleavage reaction is somewhat difficult since these compounds are unstable, volatile, or very water soluble. Thus, no great effort was made to determine all the products from the cleaved radical. It is seen from the yields in Table I that the alkyl nitrates account for the main portion of the ethyl and isopropyl radicals. Most likely the very volatile olefins were also produced from those radicals and the *tert*-butyl radical.[2] The products from the isopropyl radical are strikingly different from those from the *tert*-butyl radical since no *tert*-butyl nitrate was detected but substantial amounts of *tert*-butyl alcohol and *N*-*tert*-butylacetamide were produced. In a control run using a prereduced cerium(IV) solution to which benzaldehyde and *tert*-butyl nitrate had been added, no *tert*-butyl nitrate was recovered, but about 8.6% *tert*-butyl alcohol and 2.5% *N*-*tert*-butylacetamide were found. The rest of the *tert*-butyl moiety was either not extracted from the water layer or escaped as isobutylene. In a similar control experiment, isopropyl nitrate was found to be stable to the reaction conditions.

Discussion

The ratios of benzaldehyde to alkyl phenyl ketone that were obtained from the cerium(IV) oxidation of the alkylphenylcarbinols should give a good indication of the stability of the cleaved radical that is needed for facile cleavage of any given alcohol by cerium(IV). The high ratios of benzaldehyde to alkyl phenyl ketone that were obtained from the cerium(IV) oxidation of isopropyl- and *tert*-butylphenylcarbinol suggest that, if a radical as stable as a secondary carbon radical can be formed, oxidative cleavage will be the main pathway of oxidation of an alcohol by cerium(IV). This same conclusion has been reached for cobalt(III) oxidations of alcohols.[6] Thus cerium(IV) oxidative cleavage of bicyclo[2.2.1]heptan-2-ols and bicyclo[2.2.2]octan-2-ol, which is the only pathway of oxidation observed,[2] is compatible with this conclusion since in these bicyclic alcohols cleavage leads to a secondary carbon radical.

The relatively low ratio of benzaldehyde to ethyl phenyl ketone that was obtained from the oxidation of ethylphenylcarbinol indicates that formation of the corresponding carbonyl compound can compete with cleavage if a radical only as stable as a primary carbon radical is produced from the cleavage reaction.

Using the ratios of benzaldehyde to alkyl phenyl ketone and assuming that the rate of oxidation of the alkylphenylcarbinol to the corresponding ketone is not greatly affected by changing the alkyl group, it is seen that the rate of cleavage of the ethyl radical is 80 times as fast as that of the methyl radical, and the rates of cleavage of isopropyl and *tert*-butyl radicals are >4500 times as fast as that of the methyl radical. These results agree quite well with previously reported relative rates of cleavage of these radicals from *tert*-alkoxy radicals.[7] For example, Walling and Padwa report that the relative rates of cleavage of the isopropyl, ethyl, and methyl radicals from *tert*-alkoxy radicals at 40° are 3600, 100, and 1, respectively.[7] Hoare and Waters report that the relative rates of cleavage of the isopropyl, ethyl, and methyl radicals are 2300, 100, and 1, respectively, for the cobalt(III) oxidative cleavage of tertiary alcohols at 15°.[8]

The trend of the rates in going from a secondary radical to a primary radical to the methyl radical is certainly consistent with the stabilities of these radicals, but the magnitude of the difference may reflect the stabilities of the corresponding carbonium ions since the ρ value for the cerium(IV) cleavage of 2-aryl-1-phenylethanols[1a,3] indicates that there is a fair amount of positive charge on the carbon atom that becomes the radical in the transition state of the cleavage reaction.

(6) D. G. Hoare and W. A. Waters, *J. Chem. Soc.*, 2560 (1964).
(7) C. Walling and A. Padwa, *J. Amer. Chem. Soc.*, **85**, 1593 (1963), and references cited therein.
(8) D. G. Hoare and W. A. Waters, *J. Chem. Soc.*, 2552 (1964).

The alkyl radical which is produced in the oxidative cleavage should undergo a further one-electron oxidation to form stable products. There are three likely pathways for this oxidation: an electron transfer reaction (eq 1), a ligand transfer reaction (eq 2), and a reaction of the radical with nitrate to form a radical anion which is subsequently oxidized by a cerium(IV) to the neutral alkyl nitrate (eq 3). The fate of R^+ from the electron transfer reaction is not certain but the work of Kochi and coworkers[9] suggests that it should go largely to olefin. Substitution products such as the alkyl nitrate, the alcohol, and the acetamide, which would come from attack by nitrate ion, water, and acetonitrile, respectively, are also reasonable possibilities. In the ethyl case, only ethyl nitrate was detected. The 40% of the ethyl radical which is missing could be accounted for by ethylene which escaped and ethyl nitrate, ethyl alcohol, and *N*-ethylacetamide which remained in the water layer. In the isopropyl case, again a high yield of alkyl nitrate was obtained and 30% of the radical was not recovered, but also 2% of *N*-isopropylacetamide was detected. Since isopropyl nitrate was shown to be stable under the reaction conditions, a likely route for the formation of the *N*-isopropylacetamide is *via* the isopropyl cation formed by an electron-transfer reaction. In the *tert*-butyl case, no alkyl nitrate was detected but this does not mean that it was not formed since *tert*-butyl nitrate was shown to be unstable under the reaction conditions. However, the decomposition of an authentic sample of *tert*-butyl nitrate under the reaction conditions gave rise to only 8.6% *tert*-butyl alcohol and 2.5% *N-tert*-butylacetamide, whereas 14 and 11% of these two products were obtained from the oxidation of *tert*-butylphenylcarbinol. This suggests that a different route such as through the *tert*-butyl cation produced from an electron-transfer reaction might be responsible for the higher yields of the alcohol and acetamide. However, the small differences in yields and the impossibility of decomposing authentic *tert*-butyl nitrate under conditions exactly like those of the oxidation make this explanation uncertain. Of course, in both cases large amounts of the unrecovered *tert*-butyl radical no doubt escaped as isobutylene.

$$R\cdot + Ce^{IV} \longrightarrow R^+ + Ce^{III} \quad (1)$$

$$R\cdot + ONO_2Ce^{IV} \longrightarrow RONO_2 + Ce^{III} \quad (2)$$

$$R\cdot + ONO_2^- \longrightarrow [RONO_2]^- \xrightarrow{Ce^{IV}} RONO_2 + Ce^{III} \quad (3)$$

In summary, no firm conclusions about the relative importance of electron transfer, ligand transfer, or attack by nitrate in the oxidation of the ethyl, isopropyl, and *tert*-butyl radicals can be reached; however, the products are consistent with electron transfer becoming increasingly important in going from the primary to the tertiary radical, which is the expected trend.[9] In any case, it is of practical significance that tertiary alkyl nitrates are not products under our reaction conditions, even though high yields of similar secondary nitrates can be obtained.

Experimental Section

Methods and Materials.—Most methods and materials have been previously described.[1a] Methylphenylcarbinol, ethylphenylcarbinol, ethyl phenyl ketone, and *tert*-butylamine were obtained from Aldrich Chemical Co. Acetophenone, methyl benzoate, and isopropyl bromide were obtained from Matheson Coleman and Bell. Benzaldehyde, *tert*-butyl alcohol, isopropylamine, acetyl chloride, *tert*-butyl chloride, ethyl bromide, and silver nitrate were obtained from Baker Chemical Co. *tert*-Butyllithium was obtained from Foote Mineral. For glpc analysis a 7 ft × 0.25 in. [1,2,3-tris(2-cyanoethoxy)propane (TCED)] and a 7 ft × 0.25 in. SE-30 column was used.

Isopropylphenylcarbinol was prepared by the lithium aluminum hydride reduction of isopropyl phenyl ketone in tetrahydrofuran. An acidic work-up gave a colorless oil which was distilled to give 84% of isopropylphenylcarbinol: bp 104–106° (12 mm) [lit.[10] bp 112–113° (15 mm)]; nmr ($CDCl_3$) δ 7.18 (s, 5), 4.17 (d, 1, J = 6.5 Hz), 2.85 (s, 1), 1.80 (m, 1), and 0.90 and 0.70 (both d, total of 6 H, J = 6.5 Hz).

***tert*-Butylphenylcarbinol** was prepared from benzaldehyde and *tert*-butyllithium. The crude product was distilled at 107–110° (12 mm) and crystallized: mp 45° (lit.[11] mp 44–45°); nmr ($CDCl_3$) δ 7.20 (s, 5), 4.20 (s, 1), 2.75 (s, 1), and 0.85 (s, 9).

***tert*-Butyl phenyl ketone** was prepared by treating benzoic acid with 2 mol of *tert*-butyllithium. The crude product was distilled to give a colorless oil, yield 50%, bp 101–103° (12 mm) [lit.[12] bp 102° (12 mm)].

***N*-Isopropylacetamide** was prepared from isopropylamine and acetyl chloride. Distillation gave a colorless oil: yield 47%; bp 100° (12 mm) [lit.[13] bp 102–104° (14 mm)]; ir (CCl_4) 3450 and 1680 cm^{-1}; nmr ($CDCl_3$) δ 7.4 (broad s, 1), 4.10 and 4.00 (both septets, total of 1 H, J = 6.5 Hz), 1.97 (s, 3), and 1.15 (d, 6, J = 6.5 Hz).

***N-tert*-Butylacetamide** was prepared from *tert*-butylamine and acetyl chloride. Recrystallization of the crude product from benzene gave a 40% yield of the amide: mp 97.5–98.0° (lit.[14] mp 97–98°); ir (CCl_4) 3450 and 1680 cm^{-1}; nmr ($CDCl_3$) δ 6.7 (broad s, 1), 1.92 (s, 3), and 1.34 (s, 9).

Alkyl nitrates were prepared from the alkyl halide and silver nitrate by the method of Cheeseman.[15] The alkyl nitrates were distilled and trapped at −60°. Their spectra (CCl_4) were all nearly identical and showed strong bands at 1620 and 1300 cm^{-1} (ONO_2).

Ethyl nitrate was obtained from ethyl bromide: yield 42%; bp 87–88° (lit.[16] bp 87.2°); nmr ($CDCl_3$) δ 4.52 (q, 2, J = 7 Hz) and 1.33 (t, 3, J = 7 Hz).

Isopropyl nitrate was obtained from isopropyl bromide: yield 33%; bp *ca.* 20° (15 mm) (lit.[17] bp 101.0–101.4°); nmr ($CDCl_3$) δ 5.20 (septet, 1, J = 6.5 Hz) and 1.36 (d, 6, J = 6.5 Hz).

tert-Butyl nitrate was obtained from *tert*-butyl bromide: yield 27%; bp *ca.* 20° (15 mm) [lit.[18] bp 28° (4 mm)]; nmr ($CDCl_3$) δ 1.53 (s).

Cerium(IV) Oxidations of Alkylphenylcarbinols.—To 2.5 mmol of the alkylphenylcarbinol in 10 ml of 50% aqueous acetonitrile was added 5.0 mmol of CAN to give a homogeneous dark reddish brown solution. This solution was heated on a steam bath with stirring for a few minutes until it turned colorless or yellowish. After the reaction mixture was cooled to room temperature, an accurately weighed amount (*ca.* 2.5 mmol) of standard was added to it. To the two-phase reaction mixture was added 5 ml of saturated sodium chloride solution and the organic layer was removed. The aqueous layer was extracted three times with 5-ml portions of ether. The organic layers were combined and washed once with 5 ml of saturated NaCl solution and three times with 5-ml portions of 1 *M* sodium bicarbonate ($NaHCO_3$) solution, dried ($MgSO_4$), concentrated, and dissolved in 2 ml of ether. After this solution was analyzed by glpc, it was concentrated and dissolved in $CDCl_3$, dried ($MgSO_4$), and analyzed by nmr. In the glpc analysis, use was made of experimentally

(9) R. A. Sheldon and J. K. Kochi, *J. Amer. Chem. Soc.*, **90**, 6688 (1968), and references cited therein.

(10) V. Grignard, *Ann. Chim. Phys.*, **24** [7], 467 (1923); *Beilstein*, **6**, 523 (1923).

(11) J. Hampton, A. Leo, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **78**, 306 (1965).

(12) J. V. Nef, *Justus Liebigs Ann. Chem.*, **310**, 318 (1900).

(13) S. I. Gertler and A. P. Yerington, *U. S. Dep. Agr. Res. Service, Entomol. Res. Branch*, ARS-33-14, (1955); *Chem. Abstr.*, **50**, 7111*f* (1956).

(14) J. J. Ritter and P. P. Minieri, *J. Amer. Chem. Soc.*, **70**, 4045 (1948).

(15) G. W. H. Cheeseman, *Chem. Ind. (London)*, 281 (1954).

(16) E. G. Cowley and J. R. Partington, *J. Chem. Soc.*, 1252 (1933).

(17) H. Witzek, *Z. Phys. Chem., Abt. B*, **52**, 157 (1942).

(18) A. Michael and G. H. Carlson, *J. Amer. Chem. Soc.*, **57**, 1270 (1935).

determined correction factors for differences in relative thermal conductivities.

In order to determine the yields of the more volatile products, the work-up for some runs was changed. The organic layer that had been separated after the addition of 5 ml of saturated NaCl solution to the reaction mixture was washed once with 5 ml of saturated NaCl solution and once with 5 ml of 1 *M* $NaHCO_3$ solution. This organic layer was then dissolved in an equal volume of $CDCl_3$, dried ($MgSO_4$), and analyzed by nmr. The identification of some of the compounds was completed by addition of authentic samples to this solution.

The specific conditions and methods of analysis for each alkylphenylcarbinol are as follows.

Methylphenylcarbinol.—The reaction times were 6–8 min, the standard was methyl benzoate, and the TCEP column at 150° and the SE-30 column at 110° were used. In the run in which equal molar amounts of the alcohol and CAN were used, a solution of 10 mmol of CAN in 5 ml of water was added to 10 mmol of the alcohol in 5 ml of acetonitrile. The homogeneous dark reddish brown solution was heated on the steam bath until the color disappeared which took 5.5 min. The organic layer which formed was separated and the aqueous layer was extracted four times with 5-ml portions of ether. The combined organic layers were treated as described above and the ratio of recovered starting material to acetophenone was analyzed by nmr.

Ethylphenylcarbinol.—The reaction times were 4–5 min, the standard was acetophenone, and the TCEP column at 150° was used. In the nmr analysis for volatile products, the triplet at δ 1.30 increased and no new lines appeared when ethyl nitrate was added to the solution.

Isopropylphenylcarbinol.—The reaction times were 2–2.5 min, the standard in the analysis of the nonvolatile products was methyl benzoate, and the TCEP column at 125° was used. In the nmr analysis of the volatile products, the standard was acetophenone and the addition of isopropyl nitrate to the solution increased the intensity of the doublet at δ 1.32, but the addition of *N*-isopropylacetamide to the solution gave rise to a new doublet at δ 1.03.

***tert*-Butylphenylcarbinol.**—The reaction times were 1.5 to 2 min, the standard was acetophenone, and the TCEP column at 135° and the SE-30 column at 150° were used. In the nmr analysis of the volatile products, the addition of *tert*-butyl alcohol to the solution enhanced the singlet at δ 1.20, the addition of *N*-*tert*-butylacetamide to the solution enhanced the singlet at δ 1.31, but the addition of *tert*-butyl nitrate to the solution gave rise to a new singlet at δ 1.47.

Registry No.—Ceric ammonium nitrate, 16774-21-3; methylphenylcarbinol, 98-85-1; ethylphenylcarbinol, 93-54-9; isopropylphenylcarbinol, 611-69-8; *tert*-butylphenylcarbinol, 3835-64-1.

Fragmentation of Organic Compounds on Electron Impact. VII.[1a] Migration of Chlorine during Fragmentation of Chlorinated Norbornenes

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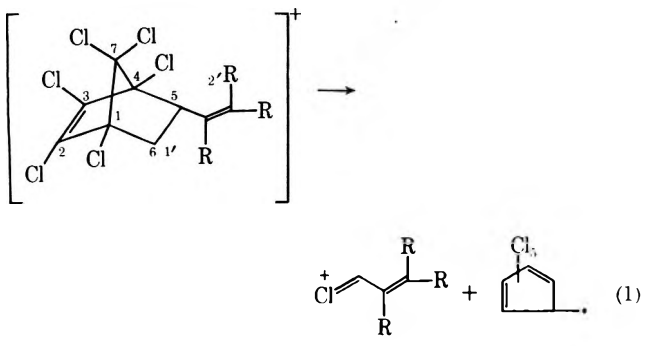
The mass spectral fragmentation patterns of a series of chlorinated norbornenes have been investigated. The compounds were prepared by the Diels–Alder reaction of chlorinated cyclopentadiene derivatives (diene component) and various monoolefins, diolefins, and aromatic olefins (dienophile component); in all cases the adduct formed in high yield and only the least hindered double bond of the dienophile entered into the reaction. Several of the compounds undergo a novel electron-impact induced rearrangement involving the migration of chlorine (eq 1). The rearranged ion is the most abundant ion in the spectrum of the styrene adduct and is present in high abundance in the spectra of various acyclic 1,3-diene adducts. The rearrangement is suppressed when a heteroatom is not attached to C-7, a methyl group is attached to C-6, or a double bond is not present at C-1′. Other fragmentations of particular interest include the elimination of the elements of the rearranged ion from the molecular ion, the formation of a trichloromethyl ion, and the retro-Diels–Alder reaction.

In recent years much effort has been devoted to the study of rearrangements of organic compounds in the mass spectrometer.[2] Most of the rearrangements involve the migration of hydrogen atoms or alkyl groups, but a number of examples are now known in which the migrating group contains a heteroatom. However, only rarely has the rearrangement of a halogen atom been detected[3] and little is known about the steric and electronic requirements of the process. We have discovered that migration of chlorine occurs with ease in certain appropriately constituted norbornenes and the fragmentation reactions of these compounds constitute the subject of this paper.



(1)

Results and Discussion

The chlorinated norbornenes shown in Table I were prepared by the Diels–Alder reaction of chlorinated cyclopentadiene derivatives (diene component) and appropriate monoolefins, diolefins, and aromatic olefins (dieneophile component); double bond isomerization does not occur; and the least hindered double bond of the dienophile reacts exclusively.

Molecular Ions.—Inspection of the partial mass spectra of the norbornenes listed in Tables II and III reveals that all of the compounds exhibit molecular ions. The relative abundance of the molecular ions, listed in Table IV, varies from 0.2 to 2.0% of Σ_{31}, with all but two of the values falling between 0.6 and 1.6% of Σ_{31}. This variation is relatively small in view of the gross structural differences of the substituent groups and reflects the moderating influence

(1) (a) Paper VI: D. S. Weinberg and M. W. Scoggins, *Org. Mass Spectrom.*, **2**, 553 (1969). (b) Glidden-Durkee, Jacksonville, Fla.

(2) R. T. Gray, R. J. Spangler, and C. Djerassi, *J. Org. Chem.*, **35**, 1525 (1970), and references cited therein.

(3) L. R. Williams, *Org. Mass Spectrom.*, **1**, 613 (1968).

TABLE I
IDENTIFICATION OF CHLORINATED NORBORNENES

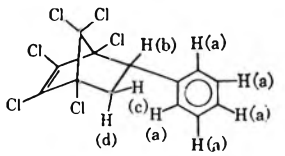
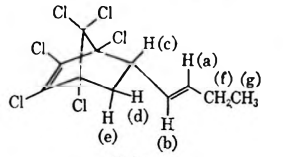
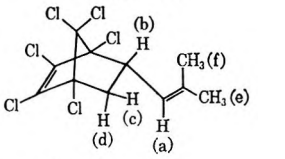
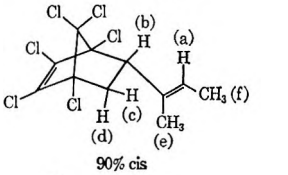
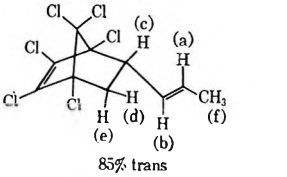
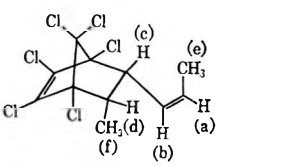
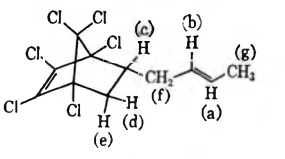
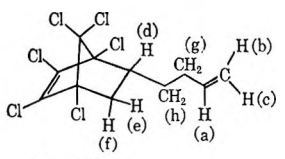
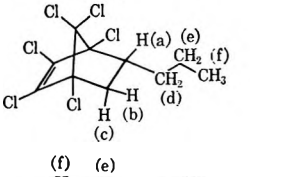
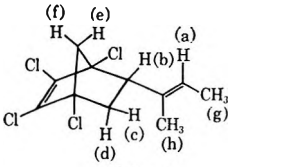
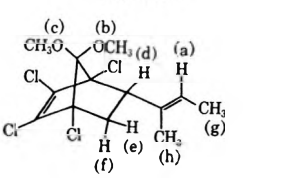
No.	Compd	Yield, %	Bp (mm), mp, °C	Analytical data
I		37	72.5–73.0	*Anal.* Calcd for $C_{13}H_8Cl_6$: C, 41.43; H, 2.14; Cl, 56.43; mol wt, 374. Found: C, 41.5; H, 2.1; Cl, 56.9; mol wt, 374. Nmr: a, τ 2.8 (5 H); b, 6.0 (1 H); c,d, 7.3, 7.4 (2 H)
II	 97% trans	80	97 (0.03)	*Anal.* Calcd for $C_{11}H_{10}Cl_6$: C, 37.23; H, 2.84; Cl, 59.43; mol wt, 352. Found: C, 37.1; H, 2.9; Cl, 59.7; mol wt, 352. Nmr: a, τ 4.3 (1 H); b, 5.0 (1 H); c, 6.7 (1 H); d, 7.3 (1 H); e,f, 8.0 (3 H); g, 9.0 (3 H)
III		61	98 (0.09)	*Anal.* Calcd for $C_{11}H_{10}Cl_6$: C, 37.23; H, 2.84; Cl, 59.93; mol wt, 352. Found: C, 36.6; H, 2.8; Cl, 60.2; mol wt, 352. Nmr: a, τ 5.3 (1 H); b, 6.3 (1 H); c, 7.3 (1 H); d,e,f, 8.2 (7 H)
IV	 90% cis	57	93 (0.03)	*Anal.* Calcd for $C_{11}H_{10}Cl_6$: C, 37.23; H, 2.84; Cl, 59.33; mol wt, 352. Found: C, 37.1; H, 2.8, Cl, 59.2; mol wt, 352. Nmr: a, τ 4.7 (1 H); b, 6.6 (1 H); c,d, 7.6, 7.7 (2 H); e,f, 8.3 (6 H)
V	 85% trans	88	78 (0.04)	*Anal.* Calcd for $C_{10}H_8Cl_6$; C, 35.23; H, 2.36; Cl, 62.48; mol wt, 338. Found: C, 35.2; H, 2.4; Cl, ...; mol wt, 338. Nmr: a, τ 4.3 (1 H); b, 5.0 (1 H); c, 6.7 (1 H); d, 7.4 (1 H); e,f 8.0, 8.3 (4 H) (distribution of peaks between τ 8.0 and 8.3 reflects presence of cis and trans isomers)
VI	 100% cis	62	92 (0.04)	*Anal.* Calcd for $C_{11}H_{10}Cl_6$: C, 37.23; H, 2.84; Cl, 59.93; mol wt, 352. Found: C, 36.9; H, 2.9; Cl, 60.0; mol wt, 352. Nmr: a, τ 4.2 (1 H); b, 5.0 (1 H); c, 6.2 (1 H); d, 7.0 (1 H); e, 8.3 (3 H); f, 9.1 (3 H)
VII		77	91 (0.03)	*Anal.* Calcd for $C_{11}H_{10}Cl_6$: C, 37.23; H, 2.84; Cl, 59.93; mol wt, 352. Found: C, 36.9; H, 2.9; Cl, 59.9; mol wt, 352. Nmr: a,b, τ 4.2–4.8 (2 H); c,d,e, 7.2–7.8 (3 H); f,g, 8.1–8.5 (5 H)
VIII		80	93 (0.05)	*Anal.* Calcd for $C_{11}H_{10}Cl_6$: C, 37.23; H, 2.84; Cl, 59.93; mol wt, 352. Found: C, 36.9; H, 2.6; Cl, 59.8; mol wt, 352. Nmr: a, τ 4.3 (1 H); b,c, 5.0 (2 H); d,e, 7.3 (2 H); f,g,h, 7.8–8.5 (5 H)
IX		96	94 (0.08)	*Anal.* Calcd for $C_{10}H_{10}Cl_6$: C, 35.02; H, 2.94; Cl, 62.03; mol wt, 340. Found: C, 34.96; H, 3.04; Cl, 60.6; mol wt, 340. Nmr: a,b, τ 7.3 (2 H); c,d,e,f, 8.0–9.0 (8 H)
X	 100% trans	72	75 (0.07)	*Anal.* Calcd for $C_{11}H_{12}Cl_4$: C, 46.19; H, 4.23; Cl, 49.58; mol wt, 284. Found: C, 46.08; H, 4.19; Cl, 49.8; mol wt, 284. Nmr: a, τ 4.7 (1 H); b, 6.8 (1 H); c,d,e,f, 7.3–8.0 (4 H); g,h, 8.4 (6 H)
XI	 100% trans	85	100 (0.05)	*Anal.* Calcd for $C_{13}H_{16}Cl_4O_2$: C 45.12; H, 4.66; Cl, 40.98; mol wt, 344. Found: C, 47.7; H, 4.5, Cl, 41.8; mol wt, 344 Nmr: a, τ 4.8 (1 H); b,c, 6.4, 6.5 (6 H); d, 6.8 (1 H); e, 7.6 (1 H); f, 8.1 (1 H); g,h, 8.3 (6 H)

TABLE II

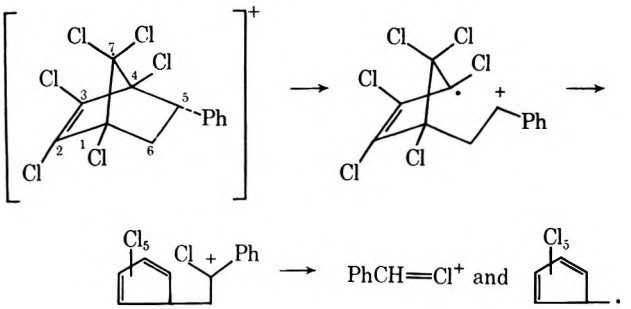
PARTIAL[a] MASS SPECTRA OF CHLORINATED NORBORNENES

m/e	Number of chlorine atoms in ion	Peak intensities I	II	III	IV	V	VI
36	1	8	6	4	4	4	1
39	0	3	13	7	7	9	5
41	0		20	12	11	9	6
53	0		8	5	7	15	5
67	0		100	43	76	26	38
68	0		5	2	4	100	2
81	0	1	2	10	13		
82	0	1	88	88	82		100
89	0					78	6
91	0	2					
103	1	10	94	100	100		
104	0	89	2	5	4		
117	3	2	1	2		1	
125	1	100					
214	4	4	3	28	11	24	
227	4		7	3	6	3	1
235	5	8	27	21	25	18	10
249	5					3	
267	3	3					
270	6	2	6	3	4	5	1
275	5		13	4		6	
281	4		11		3		
289	5				12		2
303	4	0.7				4	
316	5		5	1			
317	5		8	1	12		2
338	5	0.5				3	
339	5	0.5					
352	6		5	6	4		2
374	6	5					

[a] Only those peaks are listed which are at least 10% as intense as the base peaks or are of special interest. The latter consist of the parent peaks, various low intensity peaks relevant to the discussion of fragmentation mechanisms, and peaks of moderate intensities included for comparison. The number of chlorine atoms in each ion was determined by high resolution mass measurements or by the distribution of isotope peaks; the intensities of all the chlorine isotope peaks representing a particular chlorine-containing ion were summed and listed as a single value at the m/e value for the ^{35}Cl species in order to reduce the complexity of the table.

of the remainder of the molecule on the ionization and fragmentation processes.

Ions Formed by Rearrangement Processes.—The most abundant and significant ion in the mass spectrum of I occurs at m/e 125. It represents 28.1% of Σ_{31} and has the composition C_7H_6Cl; consequently it must be produced by a novel rearrangement. Initial fragmentation probably involves cleavage of the C-4–C-5 bond. Earlier studies of bicyclic systems have suggested that cleavage of bonds attached to the bridgehead carbon atoms are facile[4,5] and in this system such a reaction is particularly favored since both an allylic radical and allylic carbonium ion are generated in the process.[6] Migration of chlorine to C-5 then occurs followed by cleavage of the C-5–C-6 bond.



In view of the propensity of chlorine atoms to take part in five-membered transition states[7] and the op-

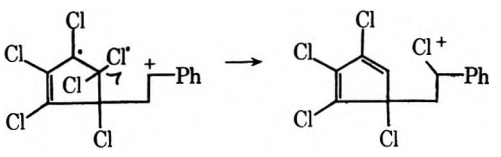


TABLE III

PARTIAL[a] MASS SPECTRA OF CHLORINATED NORBORNENES

m/e	Number of chlorine atoms in ion	Peak intensities VII	VIII	IX	X	XI
36	1	15	1	12	4	1
39	0	15	6	16	5	1
41	0	30	11	54	5	1
43	0			49	1	
53	0	12	4	5	4	2
55	0	100	7	46	2	4
59	0					9
67	0	28	15		46	7
69	0	3	1	57	2	
70	0			3	2	
81	0	28	15		7	1
82	0	8	1		100	5
83	0	3	3	7	8	
91	1			14		
99	1					23
103	1	17	3	15	12	5
117	3	14	13	23		
177	1				66	
202	4				26	
210	3					5
212	2				22	
214	4	13	33	68		
227	4	16	43	44		
235	5	15	70	77		
237	1					20
241	2					29
245	4					2
248	3				5	
249	5 (3)		19	31	(5)	
262	5 (4)		23	19		(7)
270	6	6	100	100		
272	2					7
273	2					14
277	3					16
281	4	6	35			
284	4				6	
305	5			80		
308	3					40
309	3					100
317	5	7	45			
340	6			21		
344	4					5
352	6	1	13			

[a] See Table II for criteria used to select data included in this table.

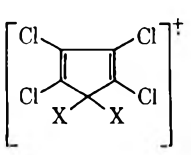
(4) D. S. Weinberg and C. Djerassi, *J. Org. Chem.*, **31**, 115 (1966).
(5) D. S. Weinberg and C. Djerassi, *ibid.*, **31**, 3832 (1966).
(6) F. W. McLafferty, "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press, New York, N. Y., 1963, Chapter 7.
(7) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967. Chapter 12.

TABLE IV

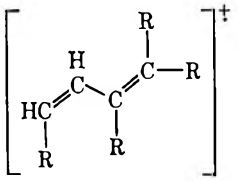
PER CENT OF Σ_{31} REPRESENTED BY SELECTED IONS

Compd no.	Per cent of Σ_{31} ions[a]						
	A	B	C	D	E	F	G
I	2.0	28.1	1.1	0.6	0.6	25.0	2.2
II	0.6	11.0	0.2	0.1	0.7	11.2	3.2
III	1.0	17.1	4.3	0.3	0.7	15.1	3.6
IV	0.6	14.8	1.6		0.6	12.3	3.7
V	0.6	15.9	5.5	0.2	1.0	20.4	3.7
VI	0.6	1.9			0.3	32.0	3.2
VII	0.2	2.8	2.1	2.3	1.0	1.3	2.5
VIII	1.5	0.3	5.7	1.5	11.3	0.1	7.9
IX	1.6	0.1	7.5	1.7	7.5	0.2	5.8
X	1.1	2.2			4.9	18.7	4.8
XI	0.8	3.6 (OCH_3) 0.8 (Cl)	1.0		1.1	0.8	1.1

[a] Identification of ions: A = molecular ion; B = rearranged ion ($RCHX^+$ where X = Cl, H, or OCH_3); C = ion A minus rearranged radical and ion A minus rearranged radical minus chlorine (A − RCHX· and A − RCHX· − Cl·); D = trichloromethyl ion; E = compound i below where X = Cl, H, OCH_3; F = compound ii below (note in compound I, this ion is $[C_6H_5CH{=}CH_2]^+$); G = ion E minus one X radical, where X = Cl, H, or OCH_3.



i



ii

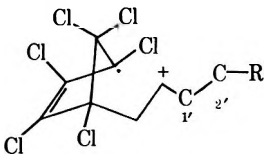
portunity for double bond formation to occur,[6] one of the chlorine atoms attached to C-7 is probably involved in the rearrangement. Evidence will be presented later that this in fact is the case.

The ion produced in the rearrangement may be a chlorotropylium ion[8] rather than a benzylic ion, but no information on this point was obtained and the behavior of compounds II to V (*vide infra*) demonstrates that the formation of a tropylium ion is not a requirement for the rearrangement.

Compounds II to IV produce rearranged ions at *m/e* 103 which represent 11.0, 17.1, and 14.8% of Σ_{31}, respectively. Compound V gives the corresponding ion at *m/e* 89 and it represents 15.9% of Σ_{31}. Hence substitution of an alkenyl group containing a double bond at C-1′ for the phenyl group does not suppress the rearrangement. The relative abundance of the rearranged ions is lower than that of the corresponding ion in the spectrum of I, but, in view of the other ions produced, this results from the cleavage of the alkyl groups before and after rearrangement rather than to a reduced tendency of the rearrangement to occur. The abundance of rearranged ions is high and indicates that the rearrangement occurs with great facility in all of these compounds.

Compound VI, which differs from compound V only by the presence of a methyl group at C-6, gives a rearranged ion at *m/e* 89 which represents only 1.9% of Σ_{31}. The low abundance of this ion underscores the extreme sensitivity of the rearrangement to the molecular structure of the compound. In this case the presence of the methyl substituent favors the retro-Diels–Alder reaction and the acylic diolefin ion at *m/e* 82 is generated which carries 32.0% of the ion current.

The rearrangement produces ions in low abundance when the alkyl substituent contains a double bond at a position other than C-1′ or when a double bond is not present. Thus, compounds VII and VIII produce rearranged ions at *m/e* 103 which represent only 2.8 and 0.3% of Σ_{31} and compound IX produces an ion at *m/e* 91 which represents only 0.1% of Σ_{31}. This behavior shows unequivocally that the double bond, although frequently mobile under electron impact conditions,[4] does not migrate sufficiently rapidly in these compounds for the isomers to lose their identity before fragmentation occurs. The fragmentation reactions which do occur produce many abundant ions and hence, unlike the situation for compound V, the rearrangement is not overshadowed by a single energetically favored competing reaction. The low abundance of rearranged ions may reflect in part the lower stability of the initial intermediate. When a C-1′ double bond



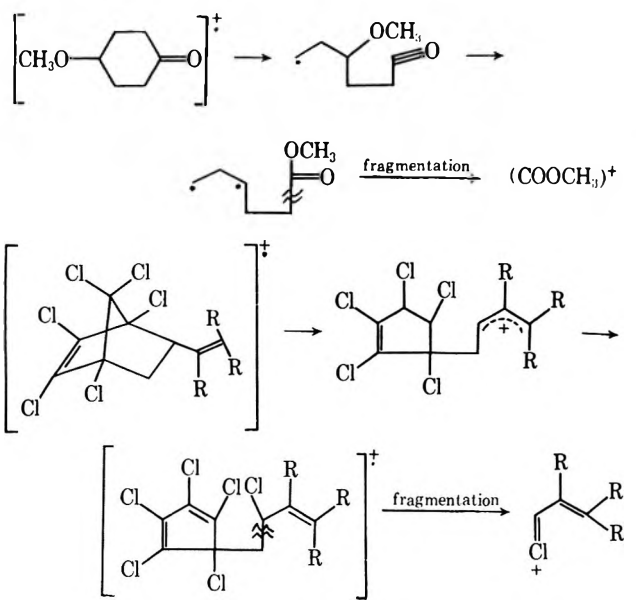
is not present, the lifetime of the intermediate may not be long enough to permit the molecule to assume the proper conformation for the transfer of chlorine, and random fragmentation of the molecule may occur instead.

Compound X, which contains two hydrogen atoms attached to C-7, produces a chlorine-containing rearranged ion at *m/e* 103 which represents only 2.2% of Σ_{31}. This species is less abundant than ten other ions produced in the fragmentation process and hence is not produced by an energetically favored process. A hydrogen-containing rearranged ion appears at *m/e* 69; it represents 0.4% of Σ_{31} but may not be produced by the specific rearrangement under consideration (a deuterium-labeled compound would have to be studied to settle this point). In addition, compound XI, which contains methoxy groups attached to C-7, produces a chlorine-containing rearranged ion at *m/e* 103 which represents 0.8% of Σ_{31} and a methoxy-containing rearranged ion at *m/e* 99 which represents 3.6% of Σ_{31}. In this case the low abundances are somewhat misleading, because a competing reaction involving the loss of chlorine dominates the fragmentation process. Thus the ion at *m/e* 99 is one of only three ions more than 20% as abundant as the ion produced in greatest yield (*m/e* 309, M − Cl). The point of importance is that a methoxy group migrates 4.5 times as often as a chlorine atom in spite of the fact that there is twice as much chlorine present in the molecule. Thus, the behavior of compounds X and XI, taken together, clearly demonstrate that the predominant rearrangement involves the migration of a heteroatom attached to C-7.

The rearrangement strikingly resembles an electron impact induced rearrangement of 4-methoxycyclohexanone disclosed several years ago.[9] In both cases, a

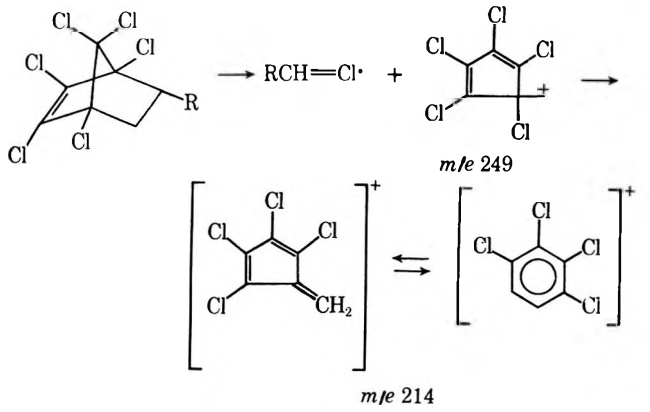
(8) S. Meyerson, "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press, New York, N. Y., 1963, Chapter 10.

(9) M. M. Green, D. S. Weinberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 3883 (1966).



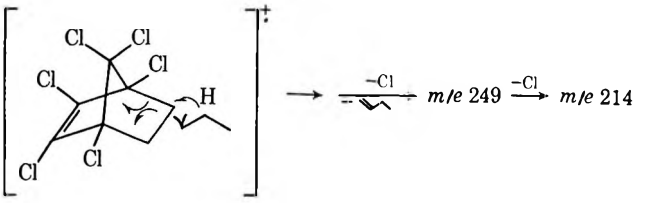
heteroatom migrates from the γ position to a stabilized carbonium ion generated by cleavage of an α-carbon bond. It is interesting that a chlorine-containing rearranged ion could not be detected in the spectrum of 4-chlorocyclohexanone studied recently in an extension of the earlier work.[2] This may reflect the instability of the rearranged acid halide rather than the poor migrating ability of chlorine. Ionized acid chlorides give molecular ions in very low abundance due to the loss of chlorine, and 4-chlorocyclohexanone produces a strong M − Cl ion.

Ions Formed by the Apparent Elimination of Rearranged Radicals and Chlorine Atoms.—All of the compounds which produce rearranged ions containing one atom of chlorine (*vide supra*) also yield ions which result from the elimination of the elements of a rearranged, chlorine-containing radical or this species plus a chlorine atom. Compound XI yields analogous ions



at *m/e* 245 and 210, respectively, the different *m/e* values resulting from the presence of a methoxy group in the ion. The abundance of the ions is low, ranging from 1 to 8% of Σ_{31}. This is at most one-third of the abundance of the ions produced by chlorine migration in compounds I to V, but 1 to 70 times higher than the abundance of these same ions in compounds VII–IV. The result for the latter series of compounds suggests that the migration of chlorine may occur to a moderate extent even when the abundance of the chlorine containing ion is low, due to charge retention by the more highly chlorinated bicyclic species.

However, it is also possible that the ions under discussion may be generated by an entirely different fragmentation reaction, such as the following. An

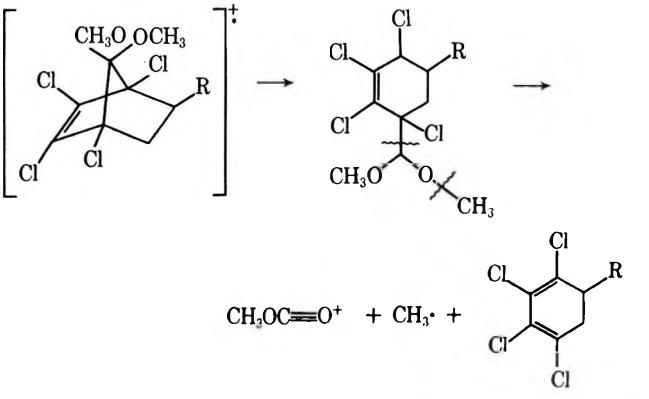


appropriate metastable peak could not be detected in support of the former mechanism and hence either mechanism may be operative.

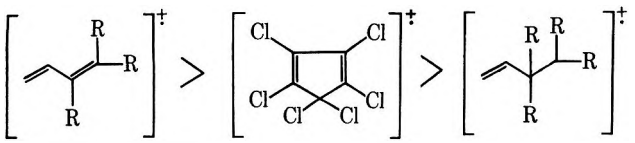
Trichloromethyl Ion.—Another rearranged ion produced by the migration of chlorine is the trichloromethyl ion. It appears in the spectra of most of the compounds at *m/e* 117 but is most abundant in the spectra of compounds VII–IX.

Since these compounds do not produce the chlorine-rearranged ion in high abundance, the dichloromethylene bridge may play an important role in this reaction, but the mechanism may be somewhat complex, since hexachlorocyclopentadiene also yields a trichloromethyl ion in low abundance.

Methoxycarbonyl Ion.—Compound XI gives an ion at *m/e* 59 which has the composition $C_2H_3O_2$ and represents 1.4% of Σ_{31}. It probably has the structure $CH_3OC{\equiv}O^+$ and may be produced as follows.

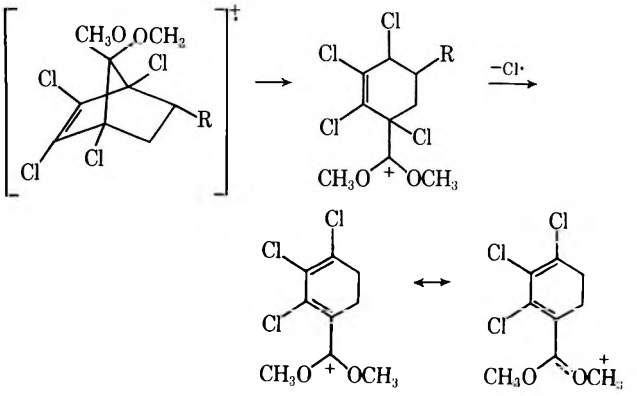


Ions Produced in the Retro-Diels–Alder Reaction.—All of the compounds included in this study undergo the retro-Diels–Alder reaction, with each fragment carrying a portion of the ion current. Acyclic conjugated olefins are produced in high abundance by compound I (*m/e* 104; 25.0% Σ_{31}), compounds II, III, IV, VI, and X (*m/e* 82; 11.2, 15.1, 12.3, 32.0, and 18.7% Σ_{31}, respectively), and compound V (*m/e* 68; 20.4% Σ_{31}), while ionized hexachlorocyclopentadiene (*m/e* 270) is produced in low abundance. The situation changes abruptly when the side chain in the molecule does not contain a double bond at C-1′. Compounds VII, VIII, and IX produce olefin fragments in low abundance at *m/e* 82 (1.3% Σ_{31}), *m/e* 82 (0.1% Σ_{31}), and *m/e* 70 (0.2% Σ_{31}), respectively, while the compounds produce hexachlorocyclopentadiene ions in moderate abundance at *m/e* 270 (1.0, 11.3, and 7.5% Σ_{31}). Since the nonconjugated olefin ions are not substantially more labile than the diolefin ions, the retro-Diels–Alder reaction generates ionized fragments in the following order of abundance.



Compound XI is capable of generating an ionized conjugated diolefin in this reaction, but it fails to produce such an ion in high abundance. This is probably due to the existence of a competing reaction which is mentioned in the next section.

Ions Formed by the Elimination of Chlorine and Hydrogen Chloride.—All of the compounds eject various combinations of chlorine and hydrogen chloride on electron impact, but only compound XI produces such ions which represent more than 9% of Σ_{31}. In the spectrum of this compound, the ion formed by the loss of a chlorine atom is the most abundant ion and the sum of the abundance of the M − Cl, M − HCl, and M − Cl − HCl ions represent 23.6% of Σ_{31}. It is apparent that special mechanisms are operative in this system, such as the following.



Experimental Section

General.—The olefins were obtained from Chemical Samples Co. or Phillips Petroleum Co. in high purity. Hexachlorocyclopentadiene was obtained from the Aldrich Chemical Co. and used without further purification. All boiling points and melting points are uncorrected. Molecular weight values were obtained from the mass spectra and are corrected for the presence of isotopic species. Nmr spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The mass spectra were obtained on a Consolidated Electrodynamics Corp. 21-110 high-resolution mass spectrometer at 70 eV. Samples were introduced through a heated inlet system at 200° into an ion source which was also maintained at 200°.

1,2,4,4-Tetrachlorocyclopentadiene-1,3.—This compound was prepared according to the procedure described by Donish[10] and was obtained in 39% yield, mp 62–63° (lit.[10] mp 61°).

1,2,3,4-Tetrachloro-5,5-dimethoxycyclopentadiene.—The procedure of McBee[11] was employed to obtain this product in 89% yield, mp 27° (lit.[11] mp 27–28°).

Diels–Alder Adducts of Hexachlorocyclopentadiene, 1,2,3,4-Tetrachlorocyclopentadiene-1,3, and 1,2,3,4-Tetrachloro-5,5-dimethoxycyclopentadine.—The chlorinated norbornenes were prepared by heating equivalent amounts of chlorinated cyclopentadiene and the appropriate olefin in a sealed glass tube for 18 hr at 95°. The yields and analyses are listed in Table I. No peaks produced by impurities could be detected in the mass spectra. The nmr spectra indicated that reaction occurs excessively between the chlorinated diene and the least hindered double bond of the acyclic olefin and that no double bond isomerization occurs.

Registry No.—I, 15584-72-2; *trans*-II, 28861-40-7; III, 28861-43-0; *cis*-IV, 28861-37-2; *trans*-V, 28861-35-0; *cis*-V, 28861-36-1; *cis*-VI, 28861-44-1; *trans*-VII, 29005-85-4; VIII, 29005-86-5; IX, 29005-87-6; *trans*-X, 29005-88-7; *trans*-XI, 29005-89-8.

(10) A. A. Donish, M. Silverman, and Y. A. Tajima, *J. Amer. Chem. Soc.*, **76**, 6144 (1954).

(11) E. T. McBee, D. L. Crain, R. D. Crain, L. R. Beloholv, and H. P. Braendlin, *ibid.*, **84**, 3557 (1962).

Electronic Effects in E2 Reactions. III. Base-Induced Eliminations of Some Phenyl 2-Pentyl Sulfones[1]

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Products of elimination have been determined for reaction of a series of 2-pentyl aryl sulfones with sodium ethylene glycolate in refluxing ethylene glycol and potassium *tert*-butoxide in refluxing pyridine. Compounds studied were *p*-nitrophenyl, *p*-bromophenyl, phenyl, *p*-methylphenyl, *p*-methoxyphenyl, 2,4,6-trimethylphenyl, and *p*-dimethylaminophenyl 2-pentyl sulfones. With a single exception (*p*-NO_2 sulfone in ethylene glycol) the proportion of 1-pentene from the base-induced eliminations was constant within the estimated limits of experimental error. In both media the ratio of *trans*- to *cis*-2-pentene from the mesityl sulfone was significantly different from that from the other sulfones. Several compounds failed to undergo base-induced elimination under these conditions. The *p*-bromophenyl sulfone was converted to *p*-hydroxyphenyl 2-pentyl sulfone in ethylene glycol and was recovered unchanged from the pyridine medium. The *p*-nitrophenyl sulfone yielded no volatile products in pyridine. The *p*-dimethylaminophenyl sulfone underwent elimination in the absence of base in both media. The results are discussed.

In recent years, the concept of a continuous spectrum of transition states for E2 reactions, differing in the extent to which the $C_\beta H$ and $C_\alpha X$ bonds are broken in the transition state, has found widespread acceptance.[2] The model has been used to account for a wide variety of structural and environmental influences on the rates and products of E2 reactions. The proposal[3] that the direction of elimination can be strongly influenced by steric factors has met with less general acceptance,

(1) (a) Abstracted from the Ph.D. Thesis of R. E. Miller, Jr., Carnegie-Mellon University, June 1967. (b) Parts I and II of this series: A. K. Colter and R. D. Johnson, *J. Amer. Chem. Soc.*, **84**, 3289 (1962); A. K. Colter and D. R. McKelvey, *Can. J. Chem.*, **43**, 1282 (1965).

(2) Recent reviews: (a) W. H. Saunders, Jr., in "The Chemistry of the Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964, Chapter 2; (b) D. V. Banthorpe in "Studies on Chemical Structure and Reactivity," J. H. Ridd, Ed., Wiley, New York, N. Y., 1966, Chapter 3; (c) J. F. Bunnett, *Surv. Progr. Chem.*, **5**, 53 (1969).

(3) H. C. Brown and I. Moritani, *J. Amer. Chem. Soc.*, **78**, 2203 (1956).

especially with regard to the importance of the steric requirements of the leaving group.[4,5]

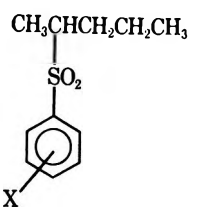
In this and previous work we have attempted to assess the importance and nature of electronic influences imposed by the leaving group in determining the products of elimination. Our approach has been to examine the products of elimination from a series of compounds differing only in a substituent in the meta or para position of a benzene ring in the leaving group. In such systems the steric requirements of the leaving group in the transition state should be constant except for small differences due to differences in solvation[6] and extent of bond fission. In earlier studies[1b] we examined the olefin mixtures from E2 reactions of a series of arenesulfonates of 2-pentanol and 2-methyl-3-pentanol. In both of these studies the composition of the olefin mixture varied in a fairly regular way with changes in the electronic nature of the leaving group, with the proportion of the more stable olefin (2-pentene and 2-methyl-2-pentene, respectively) increasing, for the most part, with increasing electron withdrawal. We interpreted these results to mean that the increasing ease of heterolysis of the C–O bond leads to a shift toward the E1-like extreme with an accompanying increase in the double bond character in the transition state.

The model of the E2 transition state elaborated by Bunnett[2c,7] does not lead to a clear-cut prediction of the effect of substitution in an arenesulfonate leaving group on the direction of elimination. Thus, it is stated[7] that a change to a leaving group of greater electron-attracting character should result in a shift toward the E1cb-like extreme while a shift toward a better leaving group should cause a shift toward the E1-like extreme.

Both of the previous studies[8] have dealt with compounds which yield predominant amounts of the more highly substituted olefin (Saytzeff pattern) under the more usual elimination conditions, presumably through transition states in the synchronous or E1-like regions. We therefore felt that it was worthwhile extending these studies to eliminations yielding predominantly the less alkylated olefin (Hofmann pattern), presumably[7] *via* transition states closer to the E1cb-like extreme. We chose for this study a series of 2-pentyl phenyl sulfones (**1**–**7**). Although the study was intended to be mainly an investigation of an electronic influences on orientation, 2-pentyl mesityl sulfone **7** was also examined.

Results

Synthesis of Sulfones.—The 2-pentyl phenyl sulfones **1**–**7** were synthesized by oxidation of the corresponding sulfide, obtained by reaction of the appropriate benzenethiol with 2-pentyl *p*-toluenesulfonate. The sulfones were characterized by elemental analysis and nmr and



1, X = *p*-$N(CH_3)_2$
2, X = *p*-OCH_3
3, X = *p*-CH_3
4, unsubstituted
5, X = *p*-Br
6, X = *p*-NO_2
7, X = 2,4,6-$(CH_3)_3$

infrared spectroscopy. The infrared spectra all showed strong absorption in the regions 1280–1300 and 1120–1140 cm^{-1}, characteristic of the sulfone function.[9]

Product Studies.—Any suitable reaction medium must be one which will induce elimination without bringing about isomerization of the olefinic products before they can be isolated. Previous studies of sulfone eliminations[4c,10–13] indicated that quite vigorous conditions would be required.

In view of the results of Hofmann, *et al.*, several attempts were made to induce elimination using *tert*-BuOK in DMSO or DMSO–*tert*-butyl alcohol mixtures. In the present work, however, no conditions were found which would yield elimination without isomerization. Reaction of the *p*-methoxyphenyl sulfone **2** in 0.2 *M* *tert*-BuOK–DMSO at 100° for 7.75 hr, followed by work-up of the reaction medium (see Experimental Section), led to recovery of *p*-hydroxyphenyl 2-pentyl sulfone in 39% yield. The rate of demethylation is therefore at least comparable to the rate of elimination under these conditions, making any estimate of the products of elimination from **2** very difficult. Basic cleavage of alkyl aryl ethers is a well-documented reaction.[14] In this case the reaction is presumably facilitated by the electron-withdrawing *p*-2-pentylsulfonyl group.

After completion of this work Bartsch and Bunnett[4c] reported a 14% yield of hexenes from 2-hexyl phenyl sulfone after 40 min in 0.5 *M* *tert*-BuOK–DMSO at 50.8° using a nitrogen bubbler and reported also that no isomerization of the hexenes occurs under these conditions.

Five of the seven sulfones were found to yield analyzable quantities of olefin in 6–8 hr using 0.4 *M* sodium ethylene glycolate (EGONa) in refluxing (bp 195–200°) ethylene glycol (EGOH). A control experiment using pure 1-pentene showed no detectable isomerization under these conditions. In all cases volatile products were collected as formed in a Dry Ice trap and analyzed by gas liquid chromatography (glc). The results of the EGONa–EGOH eliminations are summarized in Table I. With the *p*-dimethylaminophenyl, mesityl, *p*-

(4) The following authors have presented explanations based on steric influences to account for trends in the direction of elimination: (a) I. N. Feit and W. H. Saunders, Jr., *Chem. Commun.*, 610 (1967); D. L. Griffiths and D. L. Meges, *ibid.*, **90**, (1968); (c) R. A. Bartsch and J. F. Bunnett, *J. Amer. Chem. Soc.*, **91**, 1376, 1382 (1969); (d) R. A. Bartsh, *J. Org. Chem.*, **35**, 1334 (1970).

(5) The following authors have proposed steric explanations to account for other experimental observations: (a) D. H. Froemsdorf, W. Dowd, and K. E. Leimer, *J. Amer. Chem. Soc.*, **88**, 2345 (1966); (b) D. S. Bailey and W. H. Saunders, Jr., *Chem. Commun.*, 1598 (1968); (c) ref 4c; (d) I. N. Feit and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **92**, 1630 (1970).

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TABLE I

PRODUCTS OF ELIMINATION REACTIONS OF SUBSTITUTED PHENYL 2-PENTYL SULFONES IN REFLUXING ETHYLENE GLYCOL[a,b]

Phenyl substituent	Base[c]	1-Pentene, %	*trans*-2-Pentene, %	*cis*-2-Pentene, %
p-$N(CH_3)_2$	EGONa[d]	52.6	32.2	15.2
	EGONa	54.5	30.9	14.6
	None	50.6	33.7	15.7
	Quinoline	52.6	32.8	14.6
2,4,6-$(CH_3)_3$	EGONa	78.4	14.8	6.8
	EGONa	79.6	14.0	6.8
	EGONa	77.9	14.7	7.4
p-CH_3	EGONa	78.2	12.5	9.3
	EGONa	74.4	14.6	11.0
	EGONa	74.2	14.7	11.1
	EGONa	80.8	11.3	7.9
None	EGONa	75.8	14.1	10.1
	EGONa	76.3	13.6	10.1
	EGONa[e]	74.9	14.0	11.0
p-NO_2	EGONa	65.4	20.9	13.7
		59.8	25.1	15.1

[a] Gc analyses of individual mixtures considered accurate to *ca.* ±0.5% or better. [b] Concentration of sulfone, 0.2 *M*. [c] Concentration of base, 0.4 *M*, except where otherwise noted. [d] Sodium ethylene glycolate. [e] 0.8 *M*.

methylphenyl, and phenyl sulfones, **1**, **7**, **3**, and **4**, respectively, dilution of the reaction mixture with water, followed by ether extraction, yielded only unreacted sulfone, and there was no evidence for any reaction other than elimination. With the sulfones **7**, **3**, and **4** reaction occurred to the extent of roughly 2–4% per hour, based on the quantity of recovered sulfone, while the dimethylaminophenyl sulfone **1** reacted about three to six times more rapidly. The behavior of the *p*-nitrophenyl sulfone **6** was abnormal in several respects: no unreacted sulfone was recovered after 6 hr, the yield of olefins was small, and there were several unidentified volatile products formed along with the pentenes. The principal unidentified product was tentatively identified as *n*-pentane, based on glc retention times. It is clear that reactions other than base-induced elimination occur with the *p*-nitrophenyl sulfone, but we have no evidence bearing on the mechanism of formation of the pentenes. Because of the unusual reactivity of the *p*-dimethylaminophenyl sulfone **1** and the unusual composition of its elimination product, the possibility of a unimolecular elimination was examined. Surprisingly, it was found that **1** underwent elimination in refluxing EGOH, with or without added quinoline, at approximately the same rate as in the presence of alkoxide base. The olefin compositions (Table I) together with the approximate rates of reaction indicate that this sulfone undergoes elimination primarily by a mechanism not involving base, even in the presence of alkoxide. A similar control with the phenyl sulfone **4** yielded no olefin after 6.5 hr.

Reaction of *p*-bromophenyl 2-pentyl sulfone (**5**) under the usual conditions in EGONa–EGOH gave no detectable olefin after 7 hr. Dilution of the reaction mixture with water, acidification, and extraction with ether afforded a 72% yield of *p*-hydroxyphenyl 2-pentyl sulfone. This product is apparently the result of a nucleophilic displacement of bromide by EGO^- followed by basic ether cleavage as observed with the *p*-methoxyphenyl sulfone **2** in *tert*-BuOK–DMSO. In view of these results, elimination of **2** was not attempted in EGONa–EGOH.

The second medium investigated was 0.3 *M* *tert*-BuOK in refluxing (bp 113–115°) pyridine. Five of the seven sulfones afforded good yields of olefins after 6–7 hr. Again, with the exception of sulfone **6**, only unreacted sulfone could be isolated from the reaction mixture and there was no evidence for any reaction other than elimination. A control experiment with 1-pentene showed rapid liberation of the olefins with about 1% isomerization. Volatile products were again collected continuously and analyzed by glc. The results of the *tert*-BuOK–pyridine eliminations are summarized in Table II.

TABLE II

PRODUCTS OF ELIMINATION REACTIONS OF SUBSTITUTED PHENYL 2-PENTYL SULFONES IN REFLUXING PYRIDINE[a,b]

Phenyl substituent	Base[c]	1-Pentene, %	*trans*-2-Pentene, %	*cis*-2-Pentene, %
p-$N(CH_3)_2$	*tert*-BuOK[d]	79.1	14.0	6.9
	none	52.5	33.9	13.6
p-OCH_3	*tert*-BuOK	96.4	1.8	1.8
		96.3	2.0	1.7
2,4,6-$(CH_3)_3$	*tert*-BuOK	96.1	1.6	2.4
	tert-BuOK	95.9	1.6	2.5
p-CH_3	*tert*-BuOK	95.9	2.0	2.1
	tert-BuOK	95.9	2.4	1.7
None	*tert*-BuOK	95.1	2.8	2.1
	tert-BuOK	95.7	2.1	2.2

[a] Gc analyses of individual mixtures considered accurate to *ca.* ±0.5% or better. [b] Concentration of sulfone, 0.2 *M*. [c] Concentration of base, 0.3 *M*. [d] Potassium *tert*-butoxide.

While the *p*-methoxyphenyl sulfone **2** reacted normally in the refluxing pyridine medium, the *p*-bromo- and *p*-nitrophenyl sulfones **5** and **6** failed to yield any volatile products after 7 hr. The *p*-bromophenyl sulfone was recovered unchanged after this period, while the *p*-nitrophenyl sulfone was converted to unidentified dark material(s). A possible reason for the failure of **5** and **6** to eliminate under these conditions is considered below.

The dimethylaminophenyl sulfone **1** again underwent elimination in the absence of alkoxide base yielding substantial amounts of olefin in 6.5 hr. In this case the reaction in the absence of alkoxide is noticeably slower than that in the presence of alkoxide and the two product mixtures (Table II) differ substantially. Nevertheless, there is no question that a portion of the product in the presence of *tert*-BuOK is due to a mechanism not involving alkoxide. Similar control experiments with **2**, **3**, and **4** gave no detectable volatile products after 6.5 hr.

Finally, since little was known about the properties of *tert*-BuOK–pyridine as an elimination medium, elimination of 2-pentyl *p*-toluenesulfonate was carried out using conditions identical with those for the sulfone eliminations giving 66.4% 1-pentene, 23.5% *trans*-2-pentene, and 10.1% *cis*-2-pentene.

TABLE III
SUMMARY OF PRODUCTS OF BASE-INDUCED ELIMINATIONS[a]

Phenyl substituent	No. of runs	1-Pentene,[b] %	*trans*-2-Pentene,[c] %	*cis*-2-Pentene,[c] %	Trans/cis,[d] %
		EGONa in Refluxing EGOH			
2,4,6-$(CH_3)_3$	3	78.5 ± 0.5	14.5 ± 0.3	7.0 ± 0.3	2.1 ± 0.1
p-CH_3	4	76.9 ± 2.6	13.3 ± 1.4	9.8 ± 1.2	1.4 ± 0.1
None	3	75.7 ± 0.5	13.9 ± 0.2	10.4 ± 0.4	1.3 ± 0.1
p-NO_2	2	62.6 ± 2.8	23.0 ± 2.1	14.4 ± 0.7	1.6 ± 0.1
		tert-BuOK in Refluxing Pyridine			
p-OCH_3	2	96.4 ± 0.0	1.9 ± 0.1	1.7 ± 0.1	1.1 ± 0.1
2,4,6-$(CH_3)_3$	2	96.0 ± 0.1	1.6 ± 0.0	2.4 ± 0.1	0.66 ± 0.02
p-CH_3	2	95.9 ± 0.0	2.2 ± 0.2	1.9 ± 0.2	1.2 ± 0.2
None	2	95.4 ± 0.3	2.5 ± 0.4	2.1 ± 0.1	1.2 ± 0.2

[a] Averages of values listed in Tables I and II with average deviations. [b] Estimated uncertainties ±2-3% in EGOH, ±0.5% in pyridine. [c] Estimated uncertainties ±1-2% in EGOH, 0.2-0.4% in pyridine. [d] Averages and average deviations of cis/trans ratios calculated separately for each run.

Discussion

A summary of the products of the base-induced elimination is presented in Table III. For reasons not entirely understood, the reproducibility of duplicate runs in EGONa–EGOH is considerably poorer than we have obtained in previous work on arenesulfonate eliminations[1b] or in the *tert*-BuOK–pyridine eliminations. We have established *via* a control experiment using a pentene mixture that olefin fractionation is not responsible for the spread in results. We have established also (see above) that no detectable olefin isomerization occurs under the reaction conditions. It seems doubtful that the poorer temperature control achieved by the use of a refluxing solvent could lead to significant variation.

Comparison of the two base–solvent systems investigated in this work reveals a much closer adherence to the Hofmann pattern in the *tert*-BuOK–pyridine medium. This is expected either on the basis of the electronic theory[2c] (the stronger base should result in a transition state closer to the E1cb extreme and hence a greater proportion of 1-pentene) or the steric theory[15] (the proportion of 1-pentene should increase with increasing steric requirements of the base). In view of the large temperature difference, further discussion of the differences between the two reaction media does not seem warranted.

With the single exception of sulfone **6** in EGONa–EGOH the proportion of 1-pentene is independent of the phenyl substituent. Since the behavior of the *p*-nitrophenyl sulfone was abnormal in several respects (above), it does not seem safe to assume that the olefin mixture arises *via* the same mechanism as in the other cases. If the principal influence of a phenyl substituent on positional orientation is through the leaving-group inductive effect, then the products of the sulfone eliminations should be more sensitive to such substitution than the products of sulfonate elimination. If, however, the main influence is through changes in the extent of C–S (or C–O) bond fission in the transition state,[1b] then the absence of any observable effect in the sulfone eliminations is understandable. Both the strongly electron-withdrawing nature of sulfone groups and their relatively poor leaving-group properties lead to the expectation[2c,7] of a transition state near the E1cb-like extreme with very little C–S bond breaking. In line with this expectation is the strong preference for Hofmann elimination. If the extent of C–S bond fission is very small, differences in C–S bond fission between the different phenyl sulfones are also necessarily small.

It is interesting that, in spite of the invariance of the proportion of 1-pentene with leaving-group substitution, the ratio of *trans*- to *cis*-2-pentene from the mesityl sulfone **7** is out of line in both media. Particularly noteworthy is the observation that in *tert*-BuOK–pyridine the trans/cis ratio is less than 1 for the mesityl sulfone alone. Preferential formation of the less stable of a pair of geometric isomers in base-induced elimination has been reported by several groups.[4a,c,5a,d,16-18] Closely related to the present work is the observation by Bartsch and Bunnett[4c] of preferential formation of *cis*-2-hexene (over *trans*-2-hexene) from 2-hexyl phenyl sulfone in *tert*-BuOK–*tert*-BuOH and *tert*-BuOK–DMSO. In explaining this phenomenon, Brown,[18] Froemsdorf,[5a] Saunders,[5d] Bunnett,[4c] and their coworkers have ascribed an important role to the steric requirements of the leaving group. Sicher[19] and Saunders[20] have emphasized the importance of the competition between syn and anti elimination pathways in determining trans/cis ratios, and Sicher[19] has argued that steric effects *alone* cannot account for the trends in trans/cis ratios in cases where syn and anti elimination occur in competition. The present results indicate quite conclusively that trans/cis ratios can be influenced by the steric requirements of the leaving group. We have no information on the stereochemistry of the eliminations studied in this work. However, a syn mechanism for the sulfone eliminations is *a priori* not unreasonable, especially in *tert*-BuOK–pyridine, in view of the poor leaving-group, strong base, and poor ion-solvating medium.[5b,21]

The breadth of this study was severely limited by the failure of several of the sulfones to undergo base-induced elimination under the conditions investigated. Some

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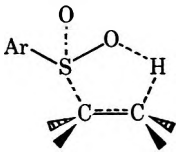
further comment on the various kinds of "abnormal" behavior is appropriate. The behavior of the *p*-methoxyphenyl sulfone **2** in *tert*-BuOK–DMSO and the *p*-bromophenyl sulfone **5** in EGONa–EGOH have been considered earlier.

The facile elimination of the *p*-dimethylaminophenyl sulfone **1** in the absence of base was unexpected. The most reasonable kind of mechanism would appear to be a unimolecular cis elimination involving a cyclic transition state **8** analogous to that generally accepted for

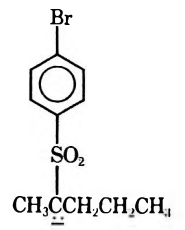


8

amine oxide and sulfoxide pyrolyses.[22,23] To our knowledge, pyrolytic elimination of sulfones has not been reported previously. Pyrolysis of simple alkyl sulfones occurs only at much higher temperatures than those studied in this work to yield sulfur dioxide together with products derived from the alkyl free radicals.[24] In view of the greater basicity of sulfoxides than sulfones,[25] it is tempting to attribute the abnormal behavior of the *p*-dimethylaminophenyl sulfone to the electron-supplying character of the dimethylamino group. If this is the case, however, it is difficult to understand the relative stability of the conjugate base of *p*-hydroxyphenyl 2-pentyl sulfone, formed in the reaction of **5** in EGONa–EGOH. Further investigations of this reaction, particularly its stereochemistry, are planned.

A possible side reaction in the case of the *p*-nitrophenyl sulfone **6** in either medium is a one-electron transfer from alkoxide or from the conjugate base of the sulfone to the sulfone to yield a radical anion. This reaction would be analogous to that proposed for *p*-nitrocumyl chloride with various nucleophiles.[26] The radical anion derived from **6** would then presumably cleave to form the *p*-nitrophenylsulfinate anion plus the 2-pentyl free radical. The latter could then produce *n*-pentane *via* hydrogen atom abstraction from solvent in EGOH.

The failure of the *p*-bromophenyl sulfone **5** to react in *tert*-BuOK–pyridine could be due to complete conversion to its conjugate base **9**. A solution of the unsubstituted sulfone **4** in pyridine shows no absorption below *ca.* 290 mμ. Addition of *tert*-BuOK results in a new band, λ_{max} 307 mμ, which we believe to be due to the conjugate base. No quantitative measurements of acidity were carried out.



9

Experimental Section[27]

Starting Materials.—Commercial 2-pentanol (Matheson Coleman and Bell, practical) was purified by fractional distillation through a 4-ft column packed with stainless steel helices. Analysis by glc using a UCON Polar[28] column showed no detectable impurities. 2-Pentyl *p*-toluenesulfonate was prepared from pure 2-pentanol and *p*-toluenesulfonyl chloride as previously described.[1b] *p*-Methoxybenzenesulfonyl chloride was prepared by the method of Morgan and Cretcher[29] and had mp 39–40° (lit.[29] 41–42°). Mesitylenesulfonyl chloride was prepared as described by Wang and Cohen,[30] mp 54–56° (lit.[30] 56–57°). *p*-*N*,*N*-Dimethylaminophenyl thiocyanate was prepared by the method of Brewster and Schroeder,[31] mp 72–74° (lit.[31] 73–74°). *p*-Methoxybenzenethiol, *p*-bromobenzenethiol, and 2,4,6-trimethylbenzenethiol were prepared from the corresponding sulfonyl chloride by reduction with zinc dust and sulfuric acid.[32] *p*-Methoxybenzenethiol[33] was obtained in 73% yield as a yellow oil. *p*-Bromobenzenethiol was obtained in 73% yield as white plates from acetone–water, mp 74.5–75.5° (lit.[34] 75°). 2,4,6-Trimethylbenzenethiol[30] was obtained in 94% yield as a colorless oil. Commercial benzenethiol (Pitt-Consol) and *p*-methylbenzenethiol (Eastman Kodak) were used without further purification. *p*-*N*,*N*-Dimethylaminothiophenol was obtained as a yellow liquid from *N*,*N*-dimethylaminophenyl thiocyanate following the procedure of Banfield.[35] *p*-Nitrobenzenethiol was prepared from *p*-nitrochlorobenzene, sulfur, and sodium sulfide by the method of Waldren and Reid,[36] mp 77–78° (lit.[36] 77°).

Preparation of Phenyl 2-Pentyl Sulfides.—All of the sulfides were prepared in the same manner. Preparation of *p*-methylphenyl 2-pentyl sulfide is typical. A 42.3-g (0.341 mol) quantity of *p*-methylbenzenethiol, 82.6 g (0.341 mol) of 2-pentyl *p*-toluenesulfonate, and 13.7 g (0.342 mol) of NaOH dissolved in the minimum amount of 95% ethanol was refluxed for 48 hr. The solution was then concentrated by evaporation of the ethanol under vacuum and then diluted with water until an oil separated. The mixture was then extracted with ether, and the ether extract was washed with aqueous sodium carbonate and water and dried over $MgSO_4$. Filtration, followed by evaporation at reduced pressure, yielded 47.3 g (72%) of yellow oil. All of the sulfides were oils and all could be vacuum distilled except for the *p*-nitrophenyl and dimethylaminophenyl sulfides. The yields were *p*-dimethylamino, 78%; *p*-methoxy, 77%; unsubstituted, 71%; *p*-bromo, 95%; *p*-nitro, 74%; 2,4,6-trimethyl, 62%. Except for the *p*-methoxy-, *p*-methyl-, and *p*-bromophenyl sulfides (below), these compounds were directly oxidized to the corresponding sulfone without complete characterization. Except for the phenyl 2-pentyl sulfone,[37] all were previously unknown. *Anal.* Calcd for *p*-methylphenyl 2-pentyl sulfide, $C_{12}H_{18}S$: C, 74.16; H, 9.33; S, 16.50. Found: C, 74.14; H, 9.15; S, 16.45. *Anal.* Calcd for *p*-methoxyphenyl 2-pentyl sulfide, $C_{12}H_{18}OS$: C, 68.52; H, 8.63; S, 15.25. Found: C, 68.71; H, 8.58; S, 15.73. *Anal.* Calcd for *p*-bromophenyl 2-pentyl sulfide, $C_{11}H_{15}BrS$: C, 50.96; H, 5.85. Found: C, 50.70; H, 5.51.

Preparation of Phenyl 2-Pentyl Sulfones.—All of the sulfones were prepared in the same manner. The preparation of 2,4,6-trimethylphenyl 2-pentyl sulfone is typical. A 17.2-g (0.068 mol) quantity of sulfide was dissolved in acetic acid and 24 ml (0.18 mol) of 30% hydrogen peroxide added. Sufficient acetic

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acid was then added to make the solution homogeneous. The solution was heated on the steam bath overnight and then diluted with water until an oil separated out. The mixture was then extracted with ether, the ether extract was washed with dilute aqueous NaOH and water, dried over $MgSO_4$, and filtered, and the ether was removed under vacuum. The residue solidified on standing. Two crystallizations from Skellysolve B gave 12.2 g (62%) of white crystals, mp 84–86°. The other sulfones were prepared in the same way except that only 2 equiv of hydrogen peroxide were used in the oxidation of the *p*-dimethylaminophenyl sulfide. The *p*-nitrophenyl sulfone had mp 44–46°. The other sulfones were oils and all but the *p*-dimethylamino sulfone could be vacuum distilled. The yields were *p*-dimethylamino, 18%; *p*-methoxy, 49%; *p*-methyl, 49%; unsubstituted, 52%; *p*-bromo, 84%; *p*-nitro, 66%. The sulfones were characterized by elemental analyses and nmr and ir spectra.

***p*-*N*,*N*-Dimethylaminophenyl 2-Pentyl Sulfone.** *Anal.* Calcd for $C_{13}H_{21}NO_2S$: C, 61.14; H, 8.29; N, 5.49. Found: C, 61.43; H, 8.32; N, 5.69. Ir (neat) 1285, 1124 cm^{-1} (SO_2).

***p*-Methoxyphenyl 2-Pentyl Sulfone.** *Anal.* Calcd for $C_{12}H_{18}O_3S$: C, 59.47; H, 7.49. Found: C, 59.43; H, 7.63. Ir (neat) 1302, 1282, 1133 cm^{-1} (SO_2).

***p*-Methylphenyl 2-Pentyl Sulfone.** *Anal.* Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02. Found: C, 63.33; H, 8.22. Ir (neat) 1289, 1136 cm^{-1} (SO_2).

Phenyl 2-Pentyl Sulfone. *Anal.* Calcd for $C_{11}H_{15}O_2S$: C, 62.23; H, 7.60; S, 15.10. Found: C, 62.43; H, 7.66; S, 15.25. Ir (neat) 1294, 1139 cm^{-1} (SO_2).

***p*-Bromophenyl 2-Pentyl Sulfone.** *Anal.* Calcd for $C_{11}H_{15}BrO_2S$: C, 45.36; H, 5.19; S, 11.01. Found: C, 45.48; H, 5.17; S, 11.12. Ir (neat) 1300, 1142 cm^{-1} (SO_2).

***p*-Nitrophenyl 2-Pentyl Sulfone.** *Anal.* Calcd for $C_{11}H_{15}NO_4S$: C, 51.34; H, 5.87; N, 5.54. Found: C, 51.58; H, 5.98; N, 5.11. Ir (neat) 1290, 1138 cm^{-1} (SO_2).

2,4,6-Trimethylphenyl 2-Pentyl Sulfone. *Anal.* Calcd for $C_{14}H_{22}O_2S$: C, 66.10; H, 8.77; S, 12.61. Found: C, 66.30; H, 8.70; S, 12.53. Ir (CCl_4) 1320, 1136 cm^{-1} (SO_2).

Reaction Media.—Commercial ethylene glycol (Fisher, purified) was dried by reaction with sodium, followed by fractionation under reduced pressure. A weighed amount of sodium was then dissolved with stirring under a nitrogen atmosphere to give a solution 0.4 *M* in base.

Commercial pyridine (Baker, analyzed) was dried by refluxing over sodium hydroxide and then distilling. Sufficient potassium *tert*-butoxide (MSA Research Corp.) was dissolved to give a 0.3 *M* solution.

Product Studies.—A measured amount of base solution was heated nearly to boiling, and sulfone was added to 0.2 *M*. The solution was then refluxed in a flask fitted to an 18-in. distilling column fitted with a Dry Ice–acetone condenser and receiver. In this manner the olefins were distilled from the refluxing reaction medium on formation. The olefins were analyzed by glc using a 50-ft column of 20% dimethylsulfolane[38] on 60–80 mesh Chromosorb P. The peak areas were measured with a planimeter. No correction was made for differences in thermal response of the olefins. The individual peaks were identified by comparison with authentic samples.

Products of Reaction of *p*-Methoxyphenyl 2-Pentyl Sulfone in *tert*-BuOK–DMSO and *p*-Bromophenyl 2-Pentyl Sulfone in EGONa–EGOH.—A 200-ml volume of a solution of 0.175 *M* *p*-methoxyphenyl 2-pentyl sulfone (8.47 g) and 0.2 *M* *tert*-BuOK in DMSO was heated at 101° for 7.75 hr. The solution was diluted with water and extracted with ether, and the ether evaporated to yield a small amount of unidentified black liquid. The aqueous layer was acidified and extracted with ether, and the extracts were washed with water and the ether evaporated to yield 3.57 g of a brown oil. Purification of 0.65 g of this material by chromatography on alumina led to 0.60 g whose nmr ($CDCl_3$) τ showed an A_2X_2 multiplet, 4 aromatic protons, centered at 2.56, $\delta_{A-X} \approx 0.67$ ppm, $J_{A-X} = 8.4$ Hz, 6.90 (m, 1), 8.0–9.3 (m, typical of 2-pentyl group, 10). A small amount (0.5 g) of the brown oil was refluxed with an excess of methyl iodide in aqueous ethanol, diluted with water, and extracted with ether, and the ether evaporated to yield a yellow liquid which was vacuum distilled. The ir and nmr spectra of this material were identical with those of *p*-methoxyphenyl 2-pentyl sulfone.

A 200-ml volume of a solution of 0.200 *M* *p*-bromophenyl 2-pentyl sulfone (11.64 g) and 0.415 *M* EGONa in EGOH was refluxed for 7.5 hr (temperature *ca.* 197°). Work-up as described above led to 5.5 g (72%) of *p*-hydroxyphenyl 2-pentyl sulfone, identified by its nmr spectrum.

Control Experiments.—A 1-ml quantity of pure (glc) 1-pentene was dissolved in 100 ml of 0.389 *M* EGONa in EGOH. The solution was then subjected to the normal reaction procedure. The distillate showed no detectable isomerization and distillation of the pentene from the reaction mixture was complete. A similar control using 0.3 *M* *tert*-BuOK in pyridine gave a distillate which analyzed for 98.8% 1-pentene, 0.2% *trans*-2-pentene, and 1.0% *cis*-2-pentene.

A solution of 8.5 g (0.033 mol) of *p*-*N*,*N*-dimethylammophenyl 2-pentyl sulfone and 8.6 g (0.067 mol) of quinoline in 165 ml of EGOH was refluxed for 3 hr, after which time the reaction was complete. The olefinic product consisted of 52.6% 1-pentene, 32.8% *trans*-2-pentene, and 14.6% *cis*-2-pentene. A solution of 8.48 g (0.04 mol) of phenyl 2-pentyl sulfone and 5.16 g (0.04 mol) of quinoline in 100 ml of EGOH was refluxed for 6.5 hr. No detectable volatile products were produced.

A solution of 5.91 g (0.0232 mol) of *p*-*N*,*N*-dimethylaminophenyl 2-pentyl sulfone in 110 ml of pyridine was refluxed for 6.5 hr yielding a mixture of olefins analyzing for 52.5% 1-pentene, 33.9% *trans*-2-pentene, and 13.6% *cis*-2-pentene. Similar controls in refluxing pyridine were carried out with phenyl, *p*-methoxyphenyl, and *p*-methylphenyl 2-pentyl sulfones. In none of these cases were any detectable volatile products produced.

Registry No.—**1**, 29182-76-1; **2**, 29182-77-2; **3**, 29182-78-3; **4**, 29182-79-4; **5**, 29182-80-7; **6**, 29182-81-8; **7**, 29182-82-9; *p*-methylphenyl 2-pentyl sulfide, 29182-83-0; *p*-methoxyphenyl 2-pentyl sulfide, 29182-84-1; *p*-bromophenyl 2-pentyl sulfide, 29182-85-2.

(38) H. S. Knight, *Anal. Chem.*, **30**, 9 (1958).

Facile Elimination of Fluoride Ion in the Dehydrohalogenation of 3-Iodo-4-(perfluoroalkyl)butanoic Acids. Preparation of Fluorinated Sorbic Acid Analogs

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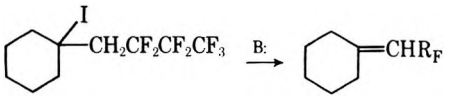
Free-radical addition of perfluoroalkyl iodides (R_FI) to 3-butenoic acid gave $R_FCH_2CHICH_2COOH$ in quantitative yield. Dehydrohalogenation of the adduct by base removed both HI and HF, forming $R_FCH_2CH{=}CHCOOH$ and $R_F'CF{=}CHCH{=}COOH$; the dienoic acid was the sole product from reaction with an excess of base. Kinetic studies showed that loss of HI preceded HF. Formation of a 1,4-dienoic acid appears to be the driving force for this reaction, since $R_FCH_2CHICH_2CH_2COOH$ with an excess of base gave only $R_FCH{=}CHCH_2CH_2COOH$.

Reactions of β-iodoperfluoroalkyl-substituted alkanes have received very little attention even though such compounds are readily obtained by the free-radical addition of perfluoroalkyl iodides to alkenes. Base-induced dehydrohalogenation of β-iodo(perfluoroalkyl)-alkanoic acids[1] (**1**) and of 1-iodo-1-heptafluorobutyl-cyclohexane[2] (**2**) gave exclusively the α,β olefin by

$$R_FCH_2\underset{\displaystyle I}{\underset{|}{C}}H(CH_2)_mCOOH \xrightarrow{B:} R_FCH{=}CH(CH_2)_mCOOH$$

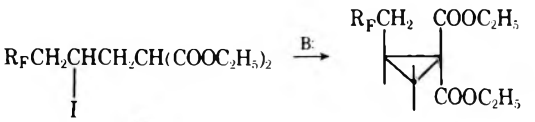
1, $m \geq 2$



2

B is a strong base, $R_F = CF_3(CF_2)_n$–, $n = 2$ and higher

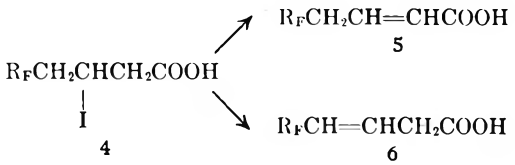
attack of the proton adjacent to the strong electron-withdrawing perfluoroalkyl (R_F) group. One exception is the malonic ester **3**, where the more highly activated



3

proton α to the ester function is attacked, giving a cyclopropane.[3] Steric hindrance or conformational effects also gave anomalous results with 1-iodo-2-(perfluoroalkyl)cycloalkanes,[4] which led to both Δ^1 and Δ^2 olefins. *In no instance has elimination of fluoride from a perfluoroalkyl group been observed.*

Reactions of $R_FCH_2CHICH_2COOH$ (**4**) presented a special problem. One might assume that dehydrohalogenation would occur *via* attack at the proton adjacent to the carboxyl group, but the evidence cited above demonstrates that the proton α to R_F is also quite acidic.



Both from the synthetic point of view and mechanistically the behavior of **4** under hydrolysis conditions appeared interesting. For reasons which will become apparent this study was extended to the nitrile, $R_FCH_2CHICH_2CN$ (**7**).

Results and Discussion

Our previously reported method[1,5] was utilized for the preparation of **4**. Azobisisobutyronitrile initiator

$$R_FI + CH_2{=}CHCH_2COOH \longrightarrow \underset{\displaystyle \mathbf{4}}{R_FCH_2CHICH_2COOH}$$

(2 mol %) at 70–80° gave quantitative yields of 3-iodo-5,5,6,6,7,7,7-heptafluoroheptanoic acid (**4**, $R_F = CF_3CF_2CF_2$) and of 3-iodo-5,5,6,6,7,7,8,8,8-nonafluoro-octanoic acid [**4**, $R_F = CF_3(CF_2)_3$–] as crystalline solids. Analogous reaction of 3-butenenitrile and 1-iodoper-fluoropropane gave 50% conversion (98% yield) of $R_FCH_2CHICH_2CN$ (**7**).

The proton nmr spectra of **4** and **7** (Chart I) were

CHART I

	δ, ppm	Lines	J, Hz
$R_FCH_2CHICH_2COOH$ (**4**)	H_4, 3.00	(6)	$J_{HF} = 20, J_{HH} = 7$
4 3 2 1	H_3, 4.52	5	$J_{H_3H_4} = 7, J_{H_2H_3} = 7$
	H_2, 3.30	2	$J_{H_2H_3} = 7$
	H_1, 11.9	1	
	H_4, 3.00	6	$J_{HF} = 20, J_{HH} = 7$
$R_FCH_2CHICH_2CN$ (**7**)	H_3, 4.50	5	$J_{H_3H_4} = 7, J_{H_2H_3} = 7$
4 3 2	H_2, 3.30	2	$J_{H_2H_3} = 7$

very similar. The six-line pattern at about δ 3.0 was partially obscured by the strong, sharp doublet of H_2 at δ 3.3. In **4** the acid proton resonance appeared at δ 11.9.

Reaction of **4** with bases was attempted under various conditions.[6] With *1 equiv* of KOH in aqueous ethanol, the solution became strongly acidic from release of HI and HF and a mixture of 5,5,6,6,7,7,7-heptafluoro-2-heptenoic acid (**5**) and 5,6,6,7,7,7-hexafluoro-*trans*,-*trans*-2,4-heptadienoic acid (**8**) (and unreacted **4**) was obtained (Scheme I).

It is postulated that the strong base (OH^-) first converted **4** to its conjugate base (**4'**) and then loss of HI by attack of another base on **4'** occurred. Similar steps resulted in elimination of HF from **5** or **6**. The stronger acids then reequilibrated with the conjugate

(1) N. O. Brace, *J. Org. Chem.*, **27**, 4491 (1962).
(2) N. O. Brace, *ibid.*, **31**, 2879 (1966).
(3) N. O. Brace, *Tetrahedron Lett.*, **20**, 1697 (1970).
(4) N. O. Brace, *J. Amer. Chem. Soc.*, **86**, 2428 (1964).
(5) N. O. Brace, to E. I. du Pont de Nemours and Co., U. S. Patent 3,145,222 (Aug 18, 1964).
(6) N. O. Brace, Abstracts of Papers, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, FLUO 42.

Scheme I

$$R_FCH_2\underset{\underset{I}{|}}{C}HCH_2COOH + OH^- \longrightarrow R_FCH_2\underset{\underset{I}{|}}{C}HCH_2COO^-$$

(4)

$$4' + B: \longrightarrow \begin{cases} R_FCH_2CH{=}CHCOO^- + HI & (5') \\ R_FCH{=}CHCH_2COO^- & (6') \end{cases}$$

$$5' \text{ or } 6' + B: \longrightarrow R_F'CF{=}CHCH{=}CHCOO^- + HF \quad (8')$$

bases present in the system to liberate the weaker carboxylic acids. Kinetics of halide elimination and product rate studies given below showed that **8** followed the formation of **5**.

When two or more equivalents of strong base were used, the conjugated dienoic acid $R_F'CF{=}CHCH{=}CHCOOH$ (**8**) was obtained in better than 95% yield; **8** was also obtained in 98% yield by the addition of 3 mol of sodium methoxide to a solution of **4** in methanol at reflux temperature. We were unable to isolate **6** from any of these reaction mixtures.

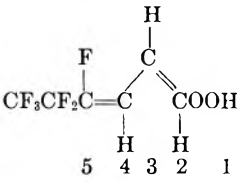
Separation of **5** and **8** proved troublesome. A mixture of **5** (40%) and **8** (60%), mp 52–53°, crystallized from the crude product mixture in ligroin. Repeated recrystallization did not change the melting point and it was unchanged by changing the solvent to CCl_4. This mixture was converted in high yield to ethyl esters **9** and **10**; nmr and ir spectra of the mixture agreed with analysis by gas–liquid phase chromatography (glpc) from which pure samples of **9** and **10** were trapped for ir spectra and analysis. $CF_3CF_2CF_2CH_2CH{=}CHCOOC_2H_5$ (**9**) thus obtained showed ν C=O 1730, ν trans C=C 1660, and characteristic bands at 982, 932, 918, and 882 cm^{-1}. A C=C stretching vibration of 1659 cm^{-1} in methyl *trans*-2-butenoate[7,8] confirms the structural assignment of **9**. The cis isomer of **9**, present in very small amount, was also trapped by glpc: ir ν C=O 1720, ν cis C=C 1650, out-of-plane CH olefinic bending at 812 cm^{-1}. Methyl *cis*-2-butenoate has reported[7] bands at ν C=O 1721, ν cis C=C 1644, and γ CH=CH 812 cm^{-1}.

Nmr spectra of **5** (or **9**) showed the anticipated six-line pattern for H_4 of **5** at δ 3.1, showing coupling with both CF_2 and adjacent vinyl proton.

	δ, ppm	Lines	J, Hz
$CF_3\overset{5}{C}F_2\overset{4}{C}H_2\overset{3}{C}H{=}\overset{2}{C}H\overset{1}{C}OOH$	H_4, 3.1	6	$J_{HF} = 18$, $J_{HH} = 8$
	$H_{2,3}$, 6.8–7.4	5	m
	H_1, 2.4	1	

Identification of **8** ($R_F' = CF_3CF_2$) as 5,6,6,7,7,7-hexafluoro-*trans*,*trans*-2,4-heptadienoic acid was based on its infrared spectrum which showed ν C=O 1710, ν C=C 1675 and 1630, and characteristic bands at 990, 962, and 895 cm^{-1}. The band at 988 cm^{-1} has been assigned to the *trans*,*trans*-diene CH rocking frequency[9] and is present in *trans*,*trans*-2,4-hexadienoic acid.[7] A band at 960 cm^{-1} is associated with CH out-of-plane vibrations in *trans*-$R_FCH{=}CHCF_3$ and $R_FCH{=}CHCH_3$.[10,11] The C=C stretching frequencies in **8** are higher than those observed for the unfluorinated acid (1642 and 1614 cm^{-1}), but this is consistent with the known effect of fluorine substitution.[8,10]

An nmr spectrum of **8** showed proton resonances of the expected complexity and shifts. The quartet at δ 7.75 could be interpreted as arising from a 16-Hz coupling of H_4 with F_5 and 11-Hz coupling of H_4 with the trans proton H_3. An 11-Hz coupling also appeared to be present in the six-line multiplet of H_2, H_3. More detailed analysis would require isolating the resonances of H_2 and H_3.



	δ, ppm	Lines	J, Hz
5 4 3 2 1	H_2H_3, 6.5	6	m
	H_4, 7.75	4	$J_{HF} = 16$, $J_{H_2H_4} = 11$
	H_1, 12.58	1	

Identification of **8** was facilitated by conversion to its ethyl ester **10**, a single substance (by glpc) obtained in 92% yield, having an ir and an nmr spectrum consistent with the postulated structure. From crude product mixtures containing **5** and **8**, ethyl esters having retention times differing from **9** and **10** were also obtained in very small amount. One such substance was an isomer of **10**, probably ethyl 5,6,6,7,7,8,8,8-octafluoro-*cis*-2-*trans*-4-octadienoate ($CF_3CF_2CF_2CF{=}CHCH{=}CHCOOC_2H_5$), having infrared bands at ν C=O 1720, ν C=C 1670 and 1605, and bands at 965 and 935 cm^{-1}. The band at 1605 cm^{-1} is at the frequency anticipated for a cis α,β double bond in this conjugated structure.[8,10]

Kinetic Studies.—In order to place these synthetic results in perspective, elimination rates of **4** under standard conditions were determined.[6] The method used previously[4] for comparison of alkyl and cycloalkyl iodides having β-perfluoroalkyl groups was employed. Two types of kinetic experiments were performed. To determine the rate of organic product formation, samples were taken at intervals, and the organic acids were extracted into CCl_4 and identified by ir spectra. In the second type of experiment, run on a micro scale, the rate of iodide elimination was followed accurately by a sensitive potentiometric titration method.[12]

The first type of experiment was limited by the fact that, at sufficiently high concentrations of **4** to permit isolation of products, reaction was too rapid to follow at the high, required base concentration. Thus, when **4** (0.2008 *M*) and NaOH (0.3984 *M*) in 92.6% ethanol at 30° were mixed, reaction occurred to the extent of 48.3% in 5 min; a mixture of **4**, **5**, and a little **8** was obtained. Further reaction occurred much more slowly as the excess alkali had been used up; in 1200 min **5** and **8** were the chief constituents (70% utilization of base). After 4010 min 88% reaction had occurred and **8** was the principal product. Second-order kinetics

(7) J. L. H. Allan, G. D. Meakins, and M. C. Whiting, *J. Chem. Soc.*, 1874 (1955).

(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 35.

(9) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass, 1966, p 104.

(10) J. K. Brown and K. J. Morgan in "Advances in Fluorine Chemistry," Butterworths, London, 1965, p 253.

(11) R. N. Haszeldine, *J. Chem. Soc.*, 2504 (1952).

(12) Assistance by Miss Gail Van Wingerden in obtaining these data is gratefully acknowledged.

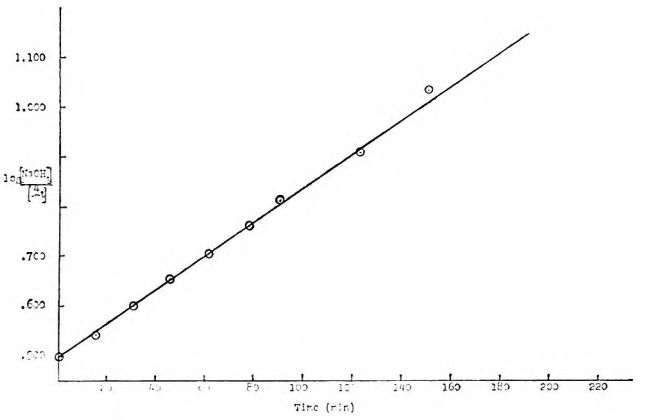


Figure 1.—Rate of iodide elimination of 4 in 92.6% ethanol at 30.0°.

were followed. The rate constant was calculated as 1.91×10^{-5} l. mol^{-1} sec^{-1} for reaction beyond 200 min, under conditions where H_2O and **4'** (or other conjugate bases) would be the expected attacking species.

In the kinetic runs on a small scale, reaction of **4** with 2 equiv of NaOH in dilute 92.6% ethanol solution at 30° was followed out to 90% iodide elimination (hydroxide ion, attacking species). Clean second-order kinetics were observed, giving good reproducibility of rate in three separate experiments. A typical plot is shown in Figure 1. Data for **4** and some related compounds are listed in Table I. The rate constant for **4**,

TABLE I
ELIMINATION RATES FOR $R_FCH_2CHICH_2COOH$ (4) AND OTHER IODO COMPOUNDS[a]

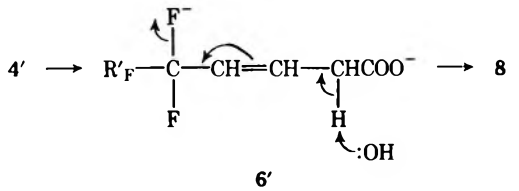
Compd	$M \times 10^3$	NaOH, $M \times 10^3$	k, l. sec^{-1} mol^{-1}
4 (run 1)	6.11	12.97	1.02×10^{-2}
4 (run 2)	5.45	12.97	1.13×10^{-2}
4 (run 3)	6.24	12.97	1.15×10^{-2}
$CF_3(CF_2)_2CH_2CHI(CH_2)_3CH_3$	5.317	12.97	4.1×10^{-2}
$CF_3(CF_2)_2CH_2CH_2I$[b]	4.89	5.016	1.55×10^{-1}
$CH_3(CH_2)_4I$[b]	157.6	279.0	5.0×10^{-5}
$CH_3CHI(CH_2)_3CH_3$	6.892	49.22	7.9×10^{-5}

[a] At 30° in 92.6% ethanol. [b] See ref 4.

$k_I = 1.10 \pm 0.05 \times 10^{-2}$, showed that under these conditions approximately 1 hr was required for half of the iodide to be eliminated. It was somewhat surprising to find that the rate for iodide elimination from iodoalkanoic acid **4** did not differ much from that from compounds such as $R_FCH_2I(CH_2)_3CH_3$ which could not form an α,β unsaturated acid. These data also showed that such β-(perfluoroalkyl)iodoalkanes reacted very much faster than unfluorinated iodoalkanes such as 1-iodopentane or 2-iodooctane. Unfortunately, comparable rate data for elimination of HI from 2-iodoalkanoic acids, RCH_2CHICH_2COOH, are not available.

In an attempt to follow the rate of fluoride ion elimination an experiment was done under identical conditions, determining the fluoride ion directly with a specific ion electrode. In 1 hr at 30°, about 20% of the expected fluoride was obtained (50% iodide elimination) confirming that the reaction proceeds, at least in part, stepwise from **5** to **8**. The order of the fluoride ion elimination reaction appeared to be complex, however.

These data cannot exclude the possibility that the sequence **4** → **6** → **8** was also being followed to a small extent. However, this is not consistent with the isolation of **5** and not **6** from a series of samples of incomplete reaction. If the rate for this process were much greater than for **5** → **8**, it would help to explain why none of **6** was found in reaction products. The postulated 1,4 elimination of HF and simultaneous shift of the double bond has not been previously observed and does not seem too likely to occur.



These results should be contrasted with those obtained by base-induced elimination of $CF_3CF_2CF_2CH_2CHI(CH_2)_2COOH$ (**1**, $m = 2$), the next higher homolog of **4**. With 2.6 mol of sodium hydroxide (1.6 M in 90% aqueous ethanol) $CF_3CF_2CF_2CH{=}CH(CH_2)_2COOH$ was the only product. There was no evidence for fluoride ion elimination, in contrast to **4**, but in agreement with previous experience.[1] The trans-olefinic $R_FCH{=}CH$ group was clearly evident from the ir spectrum, ν C=C 1675 and γ CH=CH 965 cm^{-1}, as discussed above. The nmr spectrum was consistent with the assigned structure, giving the anticipated lines and chemical shifts.

	Proton	δ, ppm
$CF_3(CF_2)_2CH{=}CHCH_2CH_2COOH$	H_3, H_3	2.52
5 4 3 2 1	H_4, H_5	5.0–6.6
	H_1	11.8

Here, of course, the acidic proton α to the carboxyl group cannot enter into the 1,2-elimination reaction, and a 1,3-conjugated diene structure would not also be conjugated with the carbonyl group. These appear to be the significant differences between **4** and $CF_3CF_2CF_2CH_2CHI(CH_2)_2COOH$.

Dehydrohalogenation of $R_FCH_2CHICH_2CN$.—In order to overcome the difficulties inherent in studying the behavior of a mixture of bases and conjugate bases of carboxylic acids, analogous reactions were carried out with 3-iodo-4-(perfluoropropyl)butanenitrile. A complex product mixture resulted which was analyzed by ir spectroscopy and separated by glpc; trapping of peaks gave 5,6,6,7,7,7-hexafluoro-*trans*,*trans*-2,4-heptadienitrile ($CF_3CF_2CF{=}CHCH{=}CHCN$) and 5,5,6,6,-7,7,7-heptafluoro-*trans*-2-heptenenitrile ($CF_3CF_2CF_2CH_2CH{=}CHCN$). Several other products were also present. An attempt to follow the kinetics of iodide elimination failed because of interference with the silver ion electrode, possibly by the nitrile group.

Experimental Section[13]

Source of Materials.—1-Iodoperfluoropropane (**11**), Pierce Chemical Co., was redistilled, bp 41°, and kept cold and dark before use. 1-Iodoperfluorobutane (**12**), bp 67°, n^{25}D 1.3248, was a gift from the E. I. du Pont de Nemours and Co. 3-Butenoic acid (**13**) and 4-pentenoic acid (**14**) from Peninsular Chem-Research Co. were fractionated in a 16-in. stainless steel spinning-

(13) Infrared spectra were recorded on a Perkin-Elmer Model 337 grating spectrometer. Nmr spectra were taken using a Varian 60 MHz A-60 spectrometer and are recorded in the format: δ in ppm (multiplet, number of protons, J = Hz, group, with protons being observed boldfaced).

band column (column A). **13**, bp 86–87° (34 mm), n^{25}D 1.4201, and **14**, bp 111–112° (50 mm), n^{25}D 1.4265, were used. Azobisisobutyronitrile (**15**), Eastman Organic Chemicals, was used as received; 3-butenenitrile (**16**) (same source) was redistilled, bp 117°, n^{25}D 1.4036.

3-Iodo-5,5,6,6,7,7,7-heptafluoroheptanoic Acid (4).—**11** (29.6 g, 0.10 mol), **13** (4.61 g, 0.050 mol), and **15** (0.164 g, 0.0010 mol) were charged into a cold Fischer-Porter Aerosol tube, cooled to −78°, evacuated, and filled with nitrogen twice. The evacuated tube was heated in an oil bath at 78 ± 1° for 21 hr and the cold liquid transferred to a flask (34.9 g, 100% recovery). Excess **11** (11.4 g) was removed *in vacuo* up to a pot temperature of 70° leaving **4** (R_F = $CF_3CF_2CF_2$) (19.8 g, 100%): mp 30–33°; ir (CCl_4) bonded OH of COOH 3500–2500, ν C=O 1710, δ CH 1425, 1400, and 1350, and bands at 1310, 1280, 1202, 1180, 1120, 965, 950, 930, and 905 cm^{-1}. A 5.0-g aliquot was distilled in two parts [no. 1, bp 78–82° (0.25 mm), n^{25}D 1.4156, 1.45 g; and no. 2, bp 82° (0.25 mm), n^{25}D 1.4173, 2.6 g] leaving undistilled product, 1.0 g. The ir spectra of the original sample and the two cuts were identical. Cut no. 2 solidified, mp 31–33°.

Anal. Calcd for $C_7F_7H_6O_2I$: C, 22.01; H, 1.58. Found: C, 22.15; H, 1.70.

3-Iodo-5,5,6,6,7,7,8,8,8-nonafluorooctanoic Acid.—**12** (35.0 g, 0.10 mol), **13** (4.61 g, 0.0535 mol), and **15** (0.164 g, 0.0010 mol) in like manner gave **4** [R_F = $CF_3(CF_2)_3$–] (24.0 g, 100%) which solidified when cooled. A 1.5-g portion of the solid was recrystallized from ligroin (bp 60–90°): mp 40°; ir (KBr plates) bonded OH of COOH, ν C=O 1710, δ CH, 1440, and 1350, ν CF 1230 and 1135, and bands at 1025, 1010, 930, 880, 840, 780, 740, 730, 690, and 685 cm^{-1}; nmr (50% CCl_4, 60 MHz) δ 3.00 (6-line multiplet, 2, partly obscured by resonance at δ 3.3, J_{HF} = 19, J_{HH} = 7 Hz, CF_2CH_2), 3.3 (d, 2, J = 7 Hz, CH_2-COOH), 4.52 (5-line multiplet, 1, J_{HH} = 7 and 7 Hz, CH_2-$CHICH_2$), and 11.9 (s, 1, COOH). Titration of 0.2104 g in 25 ml of 50% aqueous ethanol against 0.02810 *N* NaOH gave a sharp break at pH 8.3, 17.90 ml (neut equiv 418, calcd 432).

Anal. Calcd for $C_8H_6F_9O_2I$: C, 22.24; H, 1.40. Found: C, 22.49; H, 1.52.

4-Iodo-6,6,7,7,8,8,8-heptafluorooctanoic Acid (1, m = 2).—**11** (29.6 g, 0.10 mol), **14** (8.00 g, 0.080 mol), and **15** (0.246 g, 0.00150 mol) similarly gave **1** [R_F = $CF_3(CF_2)_2$, m = 2] (27.1 g, 100%), mp 42–4° before and mp 43–44.5° after carbon treatment in *n*-pentane solution, which was evaporated off and cooled: ir (KBr plates) ν C=O 1710, δ CH 1430 and 1350, ν CF 1230, 1180, and 1120, and bands at 950, 920, and 732 cm^{-1}.

Anal. Calcd for $C_8H_5F_7O_2I$: C, 24.26; H, 2.03. Found: C, 24.64; H, 2.31.

Base-Induced Elimination of 1 (m = 2).—$CF_3(CF_2)_2CH_2CHI$-$(CH_2)_2COOH$ (10.6 g, 0.030 mol) was added to a solution of NaOH (3.2 g, 0.080 mol) in 50 ml of 80% ethanol and kept at 73° for 6 hr while stirring. The product was worked up and distilled to give *cis*- and *trans*-$CF_3(CF_2)_2CH$=$CH(CH_2)_2COOH$: bp 68–69° (0.30 mm); n^{25}D 1.3620; 5.8 g (72% yield); ir (KBr) ν COOH 3300–2700, ν C=O 1715, ν C=C 1675, δ CH 1430, 1410, and 1350, and bands at 1225, 1180, 1120, 970 (s), 945 (s), 740, and 720 cm^{-1}; nmr (50%, CCl_4) δ 2.52 [s, broadened, 4, $(CH_2)_2$], 5.0–6.6 (m, 2, CH=CH), 11.8 (s, 1, COOH).

Anal. Calcd for $C_8H_7F_7O_2$: C, 35.83; H, 2.63. Found: C, 35.72; H, 2.75.

5,6,6,7,7,7-Hexafluoro-*trans,trans*-2,4-heptadienoic Acid (8, R_F' = CF_3CF_2–).—**4** (R_F = $CF_3CF_2CF_2$–) (13.3 g, 0.034 mol) in methanol (60 ml) was heated on a steam bath, and portions of sodium methoxide (5.3 g, 0.095 mol) were added during a 5-min period and then kept at 67° for 5 hr. The mixture foamed and a white precipitate formed. Water (100 ml) was added to the cooled mixture which was acidified with 10 ml of concentrated hydrochloric acid and extracted three times (25 ml v/v of ether and benzene). The organic extract was washed with water (10 ml) and dried over $MgSO_4$. Solvent was removed down to 70° (12 mm) giving CF_3CF_2CF=$CHCH$=$CHCOOH$ (**8**) (7.8 g, 98%), mp 58–63°. The reaction was repeated with identical results. Under modified conditions (see below), however, a mixture of products was obtained: ir (CCl_4) ν OH (bonded) of COOH 3100–2550, ν C=O 1702, ν CH=C 3090, ν C=C 1675 and 1625, δ CH 1420 and 1350, and bands at 1315, 1270, 1265, 1210, 1180, 1150, 1095, 990, 960, 940, 895, 732, 690, 560, and 525 cm^{-1}; nmr (20% in CCl_4) δ 5.9–6.6 (6-line unsym, 2, CH=CHCOOH), 7.65 (q, 1, J_{HH} = 11, J_{HF} = 16 Hz, CF_2CH=CH), 12.23 (s, 1, COOH). **8** sublimed at 90° (9 mm). Recrystallization from benzene and from cyclohexane containing a little benzene raised the melting point to 64–65°. No change in melting point occurred after successive recrystallizations but the mother liquors gave lower mixture melting points. Titration in 50% aqueous ethanol solution gave an equivalence point at pH 6.4.

Anal. Calcd for $C_7H_4F_6O_2$: C, 35.81; H, 1.77; neut equiv, 234.1. Found: C, 35.81; H, 1.77; neut equiv, 232 ± 1.

Alternate Methods of Dehydrohalogenation.—**4** [R_F = CF_3-$(CF_2)_2$–] (9.3 g, 0.024 mol) was added to a solution of sodium methoxide (4.5 g, 0.079 mol) in 55 ml of methanol at 45°. The temperature rose to 50° and a white solid precipitated. The mixture was heated on a steam bath at 67° for 6 hr. A yellow solution and precipitate were obtained in contrast to the colorless solution and white precipitate obtained by portionwise addition of $NaOCH_3$ (see above). The reaction mixture was worked up as above, and the solid acid was obtained as a low melting point mixture: wt 5.7 g (100%); ir ν CH=C 3090, COOH 3000–2800 (also 2720, 2680, 2620, and 2550), ν C=O 1700 (somewhat broadened), ν C=C 1625, and bands at 1410, 1350, 1320, 1275, 1250, 1220, 1180, 1150, 1095, 1035, 985, 960, 940, 890, 730, and 685 cm^{-1}. Fractional crystallization in ligroine gave a series of fractions of increasing melting point, from 45–50° to 127–135°, without achieving clean separation of products.

5,6,6,7,7,8,8,8-Octafluoro-*trans,trans*-2,4-octadienoic Acid (8, R_F' = $CF_3CF_2CF_2$).—**4** [R_F = $CF_3(CF_2)_3$–] (19.3 g, 0.045 mol) was added to a solution of 8.4 g (0.15 mol) of KOH in 100 ml of 90% aqueous ethanol and heated at 70° for 20 hr. The mixture was acidified at 10° with 15 ml of concentrated hydrochloric acid, extracted into chloroform, and dried over $MgSO_4$. A dark red mixture distilled, bp 87–120° (13 mm), 12.2 g (95%). A portion of the solid (3.6 g) in 25 ml of CCl_4 was decolorized with carbon, cooled to 10°, and gave 1.1 g, mp 69–70°; recrystallization twice gave mp 73–74°. A reaction mixture of **4** (13.0 g, 0.030 mol) and KOH (3.34 g, 0.0595 mol) in 90% ethanol (50 ml) kept at 70° for 24 hr was acidified and extracted into ether and benzene (30 ml each time) and then rinsed with aqueous sodium sulfite solution (10 ml). Evaporation of solvent gave colorless **8**, 9.1 g (100%), mp 68–70°; recrystallization from ligroine (bp 60–90°) raised the melting point to 72–73°. Titration in 50% aqueous ethanol gave an equivalence point at pH 6.4: ir (10% in CCl_4) bonded COOH 3300-2800, ν CH 3100, 3050, 3000, and 2940, (also weak bands at 2680, 2630, and 2560), ν C=O 1705, ν CH=CH 1675 and 1630, δ CH 1420, 1360, and 1330, and bands at 1280, 1260, 1240, 1220, 1190, 1130, 1065, 1040 (d), 990, 945, 915, 895, and 735 cm^{-1}; nmr (20% CCl_4) δ 6.0–6.8 (6-line multiplet, 2, unresolved, CH=CHCOOH), 7.7 (q, 1, J_{HH} = 11, J_{HF} = 16 Hz, CF=CH), 12.35 (s, 1, COOH).

Anal. Calcd for $C_8F_8H_4O_2$: C, 33.82; H, 1.42; neut equiv, 284.1. Found: C, 33.39; H, 1.46; neut equiv, 286.5.

Mixture of 5 and 8 from 4 [R_F = $CF_3(CF_2)_3$–].—**4** [R_F = CF_3-$(CF_2)_3$–] (8.65 g, 0.0200 mol), KOH (1.121 g, 0.0200 mol), and 90% ethanol (16.7 ml) kept at 70° for 24 hr became progressively darker red in color and acidic. The mixture was worked up as above and became colorless when the benzene–ether solution was rinsed with dilute sulfite solution. Evaporation of the solvent gave **4**, **5**, and **8**, 5.7 g (94%, crude). Recrystallization three times from ligroin (bp 60–90°) gave **5** and **8**, mp 52–53°, 2.6 g, and the melting point did not change when subsequently recrystallized twice from CCl_4. The ligroin filtrates were used below for esterification, and in a separate experiment the recrystallized acid mixture was also converted to ethyl esters. An infrared spectrum of the mixture clearly indicated **5** and **8** (ν C=C 1675, 1660, and 1625 cm^{-1}); nmr δ 3.1 (6-line multiplet, 1.33, J_{HF} = 18, J_{HH} = 8 Hz, CF_2CH_2 of **5**), 6.0–6.6 (6-line multiplet, 1.33, CH=CHCOOH of **8**), 6.8–7.4 (5-line multiplet, 0.66, CH=CHCOOH of **5**), 7.7 (q, 0.43, J_{HF} = 28, J_{HH} = 11 Hz, CF=CH of **8**), 12.4 (s, 1, COOH of **5** and **8**).

The mixture of **5** and **8**, mp 52–53° (0.80 g, 0.0027 mol), ethanol (5.0 ml), benzene (2.0 ml), and 1 drop of sulfuric acid was refluxed, the azeotrope removed during 8 hr, and the product worked up. The ethyl ester mixture (0.55 g) was analyzed by glpc on 10 ft × 0.25 in. Carbowax 20M (10% on Chromosorb W) and on Apiezon M (20% on Chromosorb W) columns at 130°, with 15-psi helium carrier gas. **9** [R_F = $CF_3(CF_2)_3$–] eluted at 23.8 min, 57.3% (ir matched, see below), and **10** [R_F' = $CF_3(CF_2)_2$–] eluted at 26.2 min, 37.5% (ir matched, see below).

Ethyl 5,5,6,6,7,7,7-Nonafluoro-*cis*- and -*trans*-2-octenoates.—Similarly, the ligroin filtrate (above) was converted to ethyl esters and distilled, 3.0 g. Analysis by glpc on a 10 ft × 0.25 in. silicone oil (SE-30, 10% on Chromosorb W) column as above

showed four substances: peak no. 1 at 16.5 min, 12.8%; peak no. 2 at 18.9 min, 14.4%; peak no. 3 at 23.0 min, 34.0%; peak no. 4 at 26.0 min, 39.3%. Infrared spectra confirmed that no. 3 was 9 and no. 4 was 10. Compound of peak no. 1 showed ir (CCl_4) ν CH 3050, ν C=O 1720, ν C=C 1650, δ CH 1410, 1330, and 1300, and bands at 1240, 1220, 1190, 1170, 1140, 1115, 1065, 1035, 1015 (w), 895, 855 (w), 812, and 735 cm^{-1}. From the ν C=O and ν C=C and out-of-plane CH olefinic bending frequency at 812 cm^{-1}, this substance appeared to be the cis isomer of **9**, $CF_3(CF_2)_3CH_2CH{=}CHCOOC_2H_5$, by comparison with methyl *cis*-2-butenoate[7] (ν C=O 1721, ν C=C 1644, and γ CH=CH 812 cm^{-1}). Peak no. 2 was shown to be actually two substances by analysis on 10-ft Apiezon M and silicone oil (SF-96) columns, but insufficient material was obtained for identification.

A small quantity of ethyl 5,5,6,6,7,7,8,8,8-nonafluoro-*trans*-2-octenoate (**9**) (peak no. 3) was trapped for elemental analysis and the ir spectrum showed ν CH=C 3050, ν CH 2990, 2950, 2910, 2880, ν C=O 1730, ν C=C 1660, δ CH 1475, 1465, 1448, 1425, 1380, 1370, 1350, and 1320, ν CF 1270, 1240, and 1220, and bands at 1200, 1190, 1170, 1140, 1100, 1045, 1020, 982, 945, 932, 918, 882, 860, 835, and 690 cm^{-1}.

Anal. Calcd for $C_{10}H_9F_9O_2$: C, 35.10; H, 2.65; F, 49.98. Found: C, 35.30; H, 2.44; F, 50.30.

Ethyl 5,6,6,7,7,7-Hexafluoro-*trans*,*trans*-2,4-heptadienoate (10).—**8** ($R_F' = CF_3CF_2-$) (2.58 g, 0.011 mol), ethanol (2.3 g, 0.050 mol), benzene (30 ml), and 2 small drops of sulfuric acid were heated under reflux 5 hr, while azeotrope was removed slowly. After the usual work-up procedure **10** distilled in column A: bp 80° (20 mm); $n^{25}D$ 1.3980; 2.05 g (78%); ir (CCl_4 solution or film on KBr) ν CH=C, 3095 and 3050, ν CH 3000, 2950, 2925, and 2880, ν C=O 1725, ν C=C 1675 and 1620, δ CH_3 1475 and 1360, δ CH_2 1450, 1440, and 1320, ν CF 1290, 1265, 1240, and 1215, and bands at 1170, 1140, 1095, 1045, 995, 985, 890, 865, 812, 790, 770, and 740 cm^{-1}; nmr (neat) δ 1.24 (t, 3, J = 7 Hz, CH_3), 4.21 (q, 2, J = 7 Hz, CH_2CH_3), 6.0–6.8 (6-line multiplet, 2, unresolved CH=CH), 7.5 (q, 1, J_{HH} = 11, J_{HF} = 16 Hz, CF=CH). Glpc analysis using a 6 ft × 0.25 in. Carbowax 20M (20% on Chromosorb W) column, 135°, with 12-psi helium carrier gas gave 99% area under one peak at 8.0 min.

Anal. Calcd for $C_9F_6H_8O_2$: C, 41.23; F, 43.48; H, 3.07. Found: C, 41.17; F, 43.16; H, 3.12.

Ethyl 5,6,6,7,7,8,8,8-Octafluoro-*trans*,*trans*-2,4-octadienoate (10) and Its Isomer.—**8** [$R_F = CF_3(CF_2)_3-$] (6.50 g, 0.023 mol of crude sample, mp 68–70°) esterified as above gave **10**, bp 98° (33 mm), $n^{25}D$ 1.3855, 6.6 g (92%). Glpc analysis as above gave 95.3% under one peak at 7.4 min and three other substances, 0.75%, 3.2% at 4.0 min, and 0.86%: ir (CCl_4) was the same as **10** ($R_F' = CF_3CF_2$) to 1300 cm^{-1}, ν CF 1290, 1270, and 1240, and bands at 1190, 1160, 1140, 1120, 1100, 1060, 1040, 985, 945, 920, 890, and 732 cm^{-1}; nmr δ 1.40 (t, 3 protons, J = 7 Hz, CH_3), 4.38 (q, 2 protons, J = 7 Hz, OCH_2), 6.2–7.0 (6-line multiplet, 2 protons unresolved, CH=CHCO), 7.7 (q, 1 proton, $J_{HF} = J_{HH}$ = 11 Hz, CF=CH).

The peak at 4.0-min retention time also was trapped. An ir spectrum gave ν C=O 1720, ν C=C 1670 and 1605, δ CH 1460, 1440, and 1350, and bands at 1220, 1190, 1125, 1045, 1030, 965, and 935 cm^{-1}. Bands at 1060, 1040, 985, 945, and 890 cm^{-1} in **10** were absent. These data indicate that the second substance was an isomer of **10**, possibly ethyl 5,6,6,7,7,8,8,8-octafluoro-*cis*-2-*trans*-4-octadienoate, since the 1605-cm^{-1} band is lower in the 4.0-min peak than in the 7.4-min peak.[8] Reported values are 1642 and 1614 cm^{-1} for the trans,trans isomer and 1623 and 1587 cm^{-1} for the cis,cis isomer of hexadienoic acids.[8]

Anal. Calcd for $C_{10}H_8F_8O_2$: C, 38.47; H, 2.58. Found (**10**): C, 38.25; H, 2.51.

Base-Induced Elimination of 4. Product-Rate Studies.—**4** (8.6734 g, 20.08 mmol) was added to 10 ml of 92.6% ethanol at 30.00° in a 100-ml volumetric flask, and 80.00 ml of 0.4980 *N* sodium hydroxide solution (39.84 mmol) was added and brought to volume at 30.00° (mole ratio 1.00:2.00). After 5 min, 200 min, 1080 min, and suitable intervals thereafter, a 5-ml aliquot was added to 25.00 ml of 0.1007 *N* hydrochloric acid, the separated oil extracted with three 3-ml portions of CCl_4, and the water layer titrated with 0.02810 *N* sodium hydroxide solution, using phenolphthalein indicator. Assuming that the amount of base used was equal to the amount of organic acid hydrolyzed, concentrations of alkali and acid remaining were calculated. A plot of log $[cpd]_t/[NaOH]_t$ *vs.* time after 200 min gave a straight line of slope 9.85 × 10^{-5}/min; k was calculated from the expression[4]

TABLE II

RATE OF IODIDE ELIMINATION OF 4

Time, min	$AgNO_3$, ml	% reaction	Equiv of $AgNO_3$ × 10^{-5}	$NaOH_t$ × 10^{-4}	C_t × 10^{-4} [a]
0				18.499	6.1108
15.0	0.184	18	5.5715	17.3847	4.0965
30.0	0.323	32	9.7804	16.5429	4.1547
45.0	0.423	42	12.8084	15.9373	3.5491
61.0	0.503	50	15.2308	15.4528	3.0646
77.0	0.582	58	17.6230	14.9744	2.5862
90.0	0.637	64	19.2884	14.6413	2.2531
122.5	0.723	72	21.8924	14.1205	1.7323
150.5	0.773	77	23.4064	13.8177	1.4295
255.0	0.862	86	26.1014	13.2787	0.8905

[a] C = moles of **4**.

$$k = \frac{2.303}{60[cpd]_0 - [NaOH]_0}\left(\log\frac{[NaOH]}{[cpd]} + \log(\text{slope})\right) = 1.91 \times 10^{-5}\ \text{l. mol}^{-1}\ \text{sec}^{-1}$$

Titration showed that 48.3% of NaOH had been used in 5 min, 54.5% in 200 min, 67.8% in 1080 min, and 88% in 4010 min. Ir showed **4**, **5**, and a little **8** in the 5- and 200-min samples, very little **4** in subsequent samples, and a decreasing amount of **5** after 75.9% of the base had been used. **8** was the principal product after 81% reaction. The identification of **5** was based on bands at 1040, 880, and 690 cm^{-1}; **8** gave a shoulder at 1675, sharp band at 1625, and bands at 1065, 915, and 895 cm^{-1}. The ir spectra compared closely with an analogous mixture obtained in the preparative reaction above, shown to contain only **5** and **8**.

Iodide Elimination of 4. Kinetic Studies.[4,12]—**4** (0.2640 g, 0.6111 mmol) was placed in a 100-ml volumetric flask, diluted with 50 ml of 92.6% ethanol, and equilibrated at 29.90° (mole ratio 0.248:1.00). At t = 0, 5.00 ml of 0.4922 *N* NaOH (2.46 mmol) in 92.6% ethanol was added and diluted to 100 ml with more 92.6% ethanol. At timed intervals thereafter a 5.00-ml aliquot was placed in a 250-ml beaker containing 5 ml of 1.5 *N* nitric acid, 50 ml of 2 *N* sodium sulfate solution, and about 0.1 g of sodium bisulfite. The iodide ion was titrated with 0.03028 *N* silver nitrate, using a Beckman 39261 bright silver electrode *vs.* a saturated calomel. Typical data are recorded in Table II. It was found necessary to correct the initial concentration of NaOH for the amount reacted with **4** to give the carboxylate salt of **4**. The slope and intercept obtained from least-squares treatment of the data were used to calculate k as above.[4] Three separate runs were made using different standard solutions of $AgNO_3$ and NaOH. The values of k were determined as k_1 = 1.146 × 10^{-2}, 1.128 × 10^{-2}, and 1.023 × 10^{-2} l. mol^{-1} sec^{-1}, indicating the degree of accuracy achieved. A typical plot of the data is given in Figure 1. It will be noted that with the large excess of base used hydrolysis of **4** occurred at a much faster rate than when only an equivalent or less of base was present.

Iodide Elimination Rates of 2-Iodooctane, 1-Iodopentane, and 1,1,1,2,2,3,3-Heptafluoro-5-iodononane.[12]—In similar fashion as with **4** the rates of hydrolysis of the title compounds were measured in 92.6% ethanol. Each gave good straight line plots for second-order rates. The data are summarized in Table I.

Elimination of 4. Fluoride Determination.—**4** (0.2306 g, 5.34 × 10^{-4} mol) was dissolved in 70 ml of 92.6% ethanol in a 100-ml volumetric flask equilibrated to 30.00°, and 5.00 ml of 0.4922 *N* NaOH solution was added and made up to volume. At timed intervals 5.00-ml aliquots were added to 4.00 ml of 1.5 *N* nitric acid and a few drops of sodium bisulfite solution in a separatory funnel and extracted twice with 5 ml of CCl_4, and the aqueous layer was rinsed out with water (total volume 10.00 ml). The samples were adjusted to pH 5.0, sodium acetate–acetic acid buffer was added, and the solutions were diluted to known volume. Fluoride concentration was measured directly by use of an Orion fluoride electrode. A calibration curve was prepared using solutions containing the same concentrations of ethanol and nitrate. Results are given in Table III. After analysis known amounts of fluoride were added to samples 2 and 5 and recovery was quantitative. However, samples taken after 75.0 min gave erratic results and the fluoride added after titration was not recovered quantitatively. This indicates that interference may have been present in these samples.

TABLE III
FLUORIDE DETERMINATION

Sample	Reaction time, min	Total fluoride, 10^{-6} mol	% reaction
1	16.0	3.42	(12.8)
2	30.0	3.53	13.2
3	45.0	4.21	15.8
4	60.2	5.47	20.5
5	75.0	10.8	40.5

3-Iodo-5,5,6,6,7,7,7-heptafluoroheptanenitrile (7).—**11** (30.0 g, 0.10 mol), **16** (3.35 g, 0.05 mol), and **15** (0.25 g, 0.0015 mol) were charged to a Fischer-Porter Aerosol tube, filled with nitrogen, evacuated three times at −78°, and sealed. The tube was heated for 15 hr at 72°. The product was fractionated in a 2-ft platinum spinning-band column. **11** (19.7 g, 0.066 mol) and **16** (1.67 g, 0.025 mol) were recovered, and **7**, bp 60° (0.60 mm), $n^{25}D$ 1.4148, 8.55 g (48% conversion, 98% yield), solidified on cooling to 10°: ir (10% CCl_4) ν CH 2980 and 2950, ν C≡N 2260, δ CH 1450, 1435, 1400, 1380, 1355, and 1340, ν CF 1280–1180, and bands at 1125, 1070, 1010, 990, 965, 950, 900, 845, and 830 cm^{-1}; nmr δ 3.00 (6-line multiplet, 2, J_{HF} = 20, J_{HH} = 7 Hz, CF_2CH_2CH), 3.30 (d, 2, J = 7 Hz, $CHCH_2CN$), 4.50 (5-line multiplet, 1, J = 7 Hz, CH_2CHICH_2).

Anal. Calcd for $C_7F_7H_5NI$: C, 23.15; H, 1.39; I, 34.95. Found: C, 23.34; H, 1.47; I, 35.21.

Hydrolysis of 3-Iodo-5,5,6,6,7,7,7-heptafluoroheptanenitrile (7).—**7** (4.20 g, 0.012 mol) was added to a solution of KOH (0.822 g, 0.0146 mol) in 10.0 ml of 90% aqueous ethanol and kept at 65–70° for 7 hr. Solid separated from the orange, acidic solution in the stoppered flask. Water (10 ml) was added and benzene (three 10-ml portions) and ether (10 ml) was used to extract the organic products. The red color was removed by shaking with a dilute aqueous sodium sulfite solution. Distillation in column A gave product fractions: no. 1, bp 77° (32 mm), $n^{25}D$ 1.3577, 0.80 g; no. 2, bp 82–87° (32 mm), $n^{25}D$ 1.3684, 0.60 g; no. 3, hold-up pumped over, $n^{25}D$ 1.4160, 0.95 g (total 95% recovery). Infrared spectra (KBr plates) showed that no. 1 contained principally 5,6,6,7,7,7-hexafluoro-*trans,trans*-2,4-heptadienenitrile (**17**): ν CH 3090, ν C≡N 2230 (conj), ν C=C 1680 and 1630, δ CH 1455, 1428, 1355, and 1340, and bands at 990, 980, 960, 950, 920, 880, 828, 810, 770, 750, 735, and 725 cm^{-1}. No. 2 contained both **17** and 5,5,6,6,7,7,8,8,8-heptafluoro-*trans*-2-heptenenitrile (**18**): ν CH 3080, 3010, and 2960, ν C≡N 2245 (m, unconj) and 2230 (w), ν C=C 1680 (w) and 1648 (ms), and bands at 982, 970, 960 (s), 920, 890 (w), 810, 800, 765, 760, 755, 730, 655, 635, 545, and 530 cm^{-1}. No. 3 showed only conjugated C=CCN, ν C≡N 2230 (m), ν C=C 1648 (m), and bands at 965 (m), 760 (w), 740 (m), and 730 cm^{-1}. Glpc analysis was done using a 10 ft × 0.25 in. Apiezon M column (20% on Chromosorb W), operated at 160° with 15-psi helium carrier gas. Cut no. 1 eluted 70.3% of **17** at 4.2 min, 6.1% at 5.0 min, and 22.0% of **18** at 5.5 min. Cut no. 2 eluted 28.0% of **17** at 4.2 min, 50.4% of **18** at 5.5 min, and 16.2% of **7** at 17.0 min. Cut no. 3 eluted 2.68% of **17** at 4.2 min, 19.1% of **18** at 5.5 min, and 5 peaks from **17** to 46.8 min. Taken together these results indicate that cut no. 1 was mostly **17** and **18**; cut no. 2 contained some **17**, mostly **18**, and some **7**; and cut no. 3 was a mixture of a little **17**, some **18**, **7**, and several unidentified higher boiling substances.

Registry No.—**1** (m = 2; R_F = $CF_3(CF_2)_2$), 29370-66-9; **4** (R_F = $CF_3(CF_2)_2$), 2093-44-9; **4** (R_F = $CF_3(CF_2)_3$), 29260-81-9; **5** (R_F = $CF_3(CF_2)_2$), 29260-82-0; **7** (R_F = $CF_3(CF_2)_2$), 2357-48-4; **8** (R_F' = CF_3CF_2), 29260-84-2; **8** (R_F' = $CF_3(CF_2)_2$), 29260-85-3; **8** (R_F = CF_3CF_2) ethyl ester, 29260-86-4; **9**, 29260-87-5; *cis*-**9**, 29260-88-6; **10**, 29260-89-7; *cis,trans*-**10**, 29370-67-0; **17** (R_F = CF_3CF_2), 29370-68-1; **18** (R_F = $CF_3(CF_2)_2$), 29260-90-0; *cis*-6,6,7,7,8,8,8-heptafluorooct-4-enoic acid, 29260-91-1; *trans*-6,6,7,7,8,8,8-heptafluorooct-4-enoic acid, 29260-92-2.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Sulfoxide–Carbodiimide Reactions. X.[1] Further Studies on the Mechanism of the Oxidation Reaction

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Contribution No. 82 from the Institute of Molecular Biology, Syntex Research, Palo Alto, California 94304

Received January 7, 1971

Several new pieces of evidence concerning the course of the DMSO–DCC oxidation reaction have been considered and have led to some modification of the previously proposed mechanism. By nmr studies it has been shown that, in the absence of an alcohol, the initial DMSO–DCC adduct **1** is formed in very low equilibrium concentrations. During oxidation of an alcohol using DMSO-d_6 the resulting dicyclohexylurea is found to contain one atom of deuterium. This had led to the conclusion that the abstraction of the $-SCH_3$ proton leading to the oxysulfonium ylide **3** occurs *via* an intramolecular mechanism involving either an ionic or a tetracovalent sulfur intermediate.

Previous work from this laboratory has demonstrated that efficient oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones can be achieved under mild conditions through reaction with dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) in the presence of an appropriate proton source.[2,3] These same reagents also effect interesting, mechanistically related reactions with phenols,[4] enols,[5] oximes,[6] and a variety of other nucleophilic nitrogenous functional groups.[7]

The mechanism originally proposed[2a] for the oxidation of alcohols is outlined in Scheme I below and both the initial formation of the DMSO–DCC adduct **1** and the intramolecular nature of the proton abstraction step *via* the oxysulfonium ylide **3** have been confirmed by isotope experiments.[8]

(1) For part IX, see U. Brodbeck and J. G. Moffatt, *J. Org. Chem.*, **35**, 3552 (1970).

(2) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661 (1965); (b) *ibid.*, **87**, 5670 (1965).

(3) For a review, see J. G. Moffatt in "Techniques and Applications in Organic Synthesis: Oxidation," Vol. 2, Marcel Dekker, New York, N. Y., in press.

(4) (a) M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5855 (1966); (b) *ibid.*, **89**, 4725 (1967).

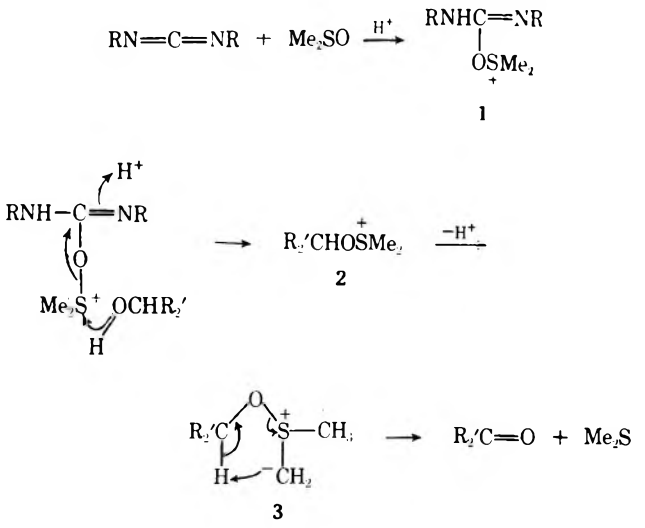
(5) A. F. Cook and J. G. Moffatt, *ibid.*, **90**, 740 (1968).

(6) A. H. Fenselau, E. H. Hamamura, and J. G. Moffatt, *J. Org. Chem.*, **35**, 3546 (1970).

(7) U. Lerch and J. G. Moffatt, unpublished results.

(8) A. H. Fenselau and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 1762 (1966).

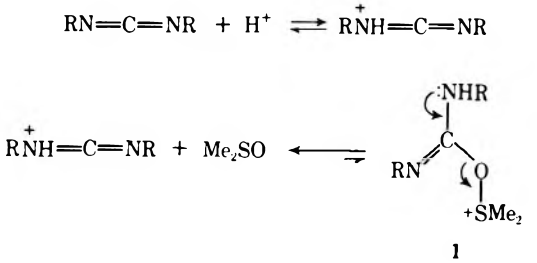
SCHEME I



While formation of the adduct **1** was unequivocally demonstrated[8] by the isolation of ^{18}O-dicyclohexylurea from an oxidation reaction using ^{18}O-DMSO, we have been unable to demonstrate the accumulation of this intermediate by nmr spectroscopy. Thus, the nmr spectrum of a solution of diisopropylcarbodiimide[9] (0.3 mmol) and DMSO (0.6 mmol) in deuteriochloroform shows only the expected signals of the individual compounds, the isopropyl groups appearing as a 6-proton doublet (J = 6 Hz) at 1.20 ppm and a 1-proton quintet (J = 6 Hz) at 3.55 ppm and the DMSO as a singlet at 2.62 ppm. Upon addition of 0.06 mmol of dichloroacetic acid there were essentially no changes in the spectrum scanned at intervals during 10 min except for the formation of small amounts of diisopropylurea (1.10 ppm, d, J = 6 Hz) and *N*-dichloroacetyl-*N*,*N'*-diisopropropylurea (1.47 ppm, d, J = 6 Hz). There was no observable change in the $-SCH_3$ resonance of the DMSO and no signal was observed in the 3.3-ppm region where oxysulfonium salts are known to appear.[10] Subsequent addition of *p*-nitrobenzyl alcohol (0.1 mmol) led to rapid oxidation to *p*-nitrobenzaldehyde, once again with no observable oxysulfonium intermediate in the 3.3-ppm range.

The lack of any observable accumulation of an oxysulfonium intermediate such as **1** upon mixing DMSO, DCC, and dichloroacetic acid in the absence of an alcohol suggests that this is a reversible process with the equilibrium lying far on the side of starting materials as in Scheme II. Such an equilibrium might well

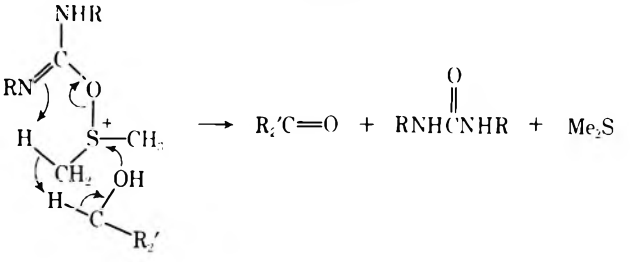
SCHEME II



be expected since the inductive effect of the positively charged sulfur in **1** would act as a driving force leading toward regeneration of DMSO and protonated carbodiimide. Since subsequent addition of an alcohol leads rapidly to oxidation without accumulation of any oxysulfonium intermediates, the formation and collapse of species such as **2** and **3** must be rapid.

In the course of his studies on the chemistry of oxysulfonium salts, Torssell[10,11] has considered the role of these compounds as intermediates in the oxidation reaction. In these studies pure samples of independently prepared isobutyloxysulfonium tetraphenylborate were reacted with DMSO, DCC, and pyridinium trifluoroacetate under conditions similar to those used successfully for oxidation of the free alcohol to the aldehyde. Examination of the reaction mixture by gas–liquid chromatography showed the presence of isobutyraldehyde and isobutyl alcohol in a ratio of 1:2 but the aldehyde could be isolated as its dinitrophenylhydrazone in only 10% yield. Attempts to isolate an oxysulfonium salt from the reaction mixture during oxidation of the alcohol were unsuccessful and, on the basis of these observations, Torssell has concluded that free oxysulfonium salts cannot be intermediates in the oxidation pathway. In order to accommodate this conclusion, Torssell has proposed a "three-body mechanism" as shown in Scheme III in which attack

SCHEME III



of the alcohol upon the DMSO–DCC adduct is accompanied by abstraction of a proton from the $S-CH_3$ group by the incipient dicyclohexylurea nitrogen and leads directly to products without intervention of the oxysulfonium salt **2**.

As proposed by Torssell[10,11] this mechanism, which involves nucleophilic attack, two proton abstractions, and collapse to products, is considered to be a concerted process and this has been criticized by Capon *et al.*,[12] on electronic grounds. There is also some doubt that the experiment using pre-formed alkoxysulfonium tetraphenylborates as described by Torssell is an entirely valid one. Our earlier work has clearly shown that the oxidation reaction is extremely sensitive to the nature of the proton source used, with neither very strong (*e.g.*, trifluoroacetic or mineral acids) or very weak (*e.g.*, acetic acid) acids being suitable. The pyridine salts of some acids give excellent results but in other cases the reactions are slow and incomplete. Since tetraphenylboric acid, while unknown as a free compound, is considered to be a strong acid,[13] it is not at all certain that the reduced yield of isobutyral-

(9) This compound is generally as good as DCC in oxidation reactions but offers the advantages of a much sharper nmr signal and a more soluble urea product.

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

(11) K. Torssell, *Tetrahedron Lett.*, 4445 (1966).

(12) B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms 1967," Interscience, New York, N. Y., 1968, p 426.

(13) J. N. Cooper and R. E. Powell, *J. Amer. Chem. Soc.*, **85**, 1590 (1963).

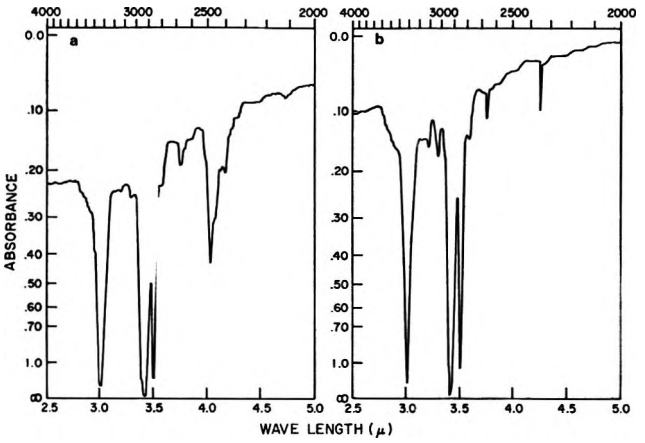


Figure 1.—Infrared spectra of dicyclohexylurea as KBr pellets: (a) dicyclohexylurea obtained following oxidation of testosterone in DMSO-d_6 (see Experimental Section); (b) unlabeled dicyclohexylurea.

dehyde is sufficiently meaningful to draw mechanistic conclusions.

The intramolecular proton abstraction from the S–CH_3 group is, however, an attractive feature of the Torssell mechanism that is amenable to experimental verification. This question appeared to be answered when Harmon and Zenarosa[14] briefly reported that an oxidation reaction using DMSO-d_6 led to the isolation of monodeuteriodicyclohexylurea thus supporting an intramolecular proton abstraction similar to that of Scheme III. Subsequently, however, these same authors, without reference to their earlier work, have reported that a similar experiment gives dicyclohexylurea which contains no deuterium.[15] The absence of deuterium appears to be based solely upon the infrared spectrum of the product and no experimental details are given as to how the reaction was worked up in order to avoid deuterium–proton exchange of the reactive N–D bond. On the basis of this latter result, Harmon, *et al.*,[15] have ruled out the Torssell mechanism (Scheme III) and favored our original proposal (Scheme I).

Prior to the appearance of the second paper from Harmon,[15] we too have examined the oxidation of an alcohol in DMSO-d_6 taking pains to exclude as much as possible the probability of exchange reactions. Thus, we have oxidized testosterone in a mixture of DMSO-d_6 and benzene using DCC and a small amount (0.24 molar equiv) of dichloroacetic acid. After 10 min the mixture was diluted with benzene and the resulting crystalline dicyclohexylurea was removed by filtration and washed carefully with dry benzene. The yield of dicyclohexylurea was, as is usually the case, somewhat in excess of theory, and thin layer chromatography of the filtrate showed that quantitative oxidation of testosterone to androst-4-ene-3,17-dione had taken place. The infrared spectrum of the dicyclohexylurea (Figure 1a) showed a fairly intense peak at 2475 cm^{-1} characteristic of an N–D stretching frequency[16] that is not present in unlabeled dicyclohexylurea (Figure 1b).

(14) R. E. Harmon and C. V. Zenarosa, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, No. D3.

(15) R. E. Harmon, C. V. Zenarosa, and S. K. Gupta, *Tetrahedron Lett.*, 3781 (1969).

(16) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 207.

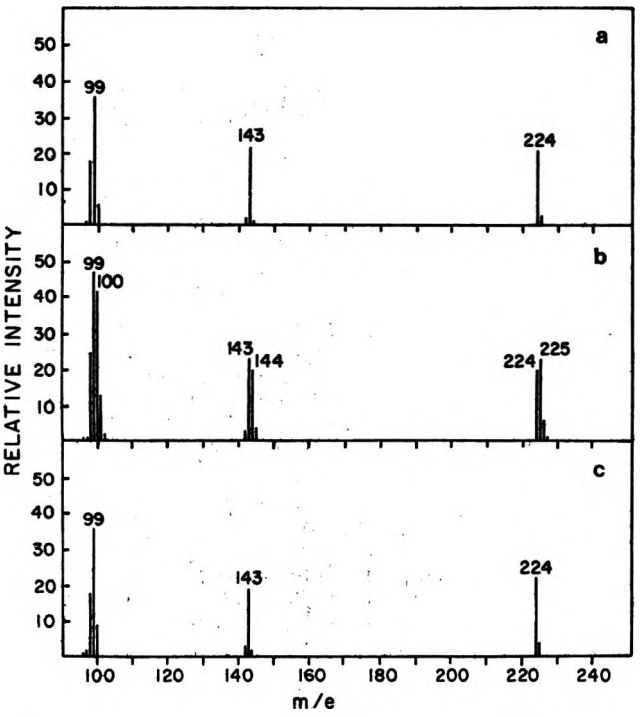


Figure 2.—Mass spectra (70 eV) of dicyclohexylurea: (a) unlabeled dicyclohexylurea; (b) dicyclohexylurea obtained following oxidation of testosterone in DMSO-d_6 (see Experimental Section); (c) dicyclohexylurea obtained from a control reaction without an added alcohol (see Experimental Section).

More compelling evidence for the incorporation of deuterium was obtained by mass spectrometry. The mass spectrum (70 eV) of unlabeled dicyclohexylurea (Figure 2a) shows a molecular ion at *m/e* 224 with a small natural abundance isotope peak (roughly 14% as intense) at *m/e* 225. The spectrum, under identical conditions, of the dicyclohexylurea isolated from the oxidation reaction is shown in Figure 2b which clearly indicates that the predominant molecular ion is now at *m/e* 225 indicating the incorporation of a single deuterium atom. The presence of a very small peak at *m/e* 227 suggests that even a trace of a dideuterio species might be present and, after correction for natural isotope abundance, the mondeuterio and nondeuterated species were estimated to be present in a ratio of 1.1:1. The incorporation of a single deuterium atom can also be seen in the fragments at *m/e* 144 ($M^+ - C_6H_9$) and *m/e* 100 $[C_6H_{11}NDH]\cdot^+$.

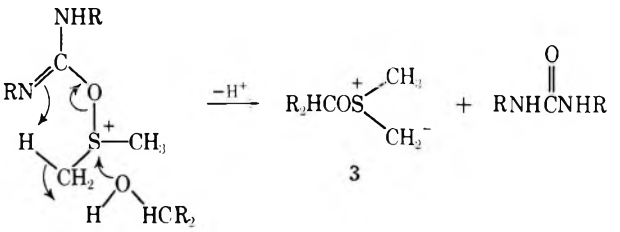
As a control for any possible exchange reactions that could lead to deuterium incorporation independent of the oxidation reaction, a similar reaction was set up without addition of any testosterone. Under these conditions only a small amount of dicyclohexylurea crystallized from the reaction mixture and after 40 min it was collected and washed with benzene as above. The mass spectrum of this material (Figure 2c) was essentially identical with that of the nondeuterated reference sample (Figure 2a) and suggested the presence of only a trace of deuterium. The fact that only about one-half of the isolated dicyclohexylurea contained deuterium suggests that decomposition of DCC to the urea can also take place through simple acid-catalyzed reactions quite independent of oxidation. This is confirmed by the isolation of the unlabeled urea in the absence of an alcohol and leads to the con-

clusion that the oxidation reaction is probably accompanied by a stoichiometric transfer of deuterium.

The experiments above quite conclusively show that the abstraction of a $(CH_3)_2S^+OR$ proton leading to the oxysulfonium ylide **3** is indeed facilitated by the nitrogen of the incipient dicyclohexylurea as suggested by Torssell and are in contrast with the conclusions of Harmon, *et al.*[15]

These observations can be accommodated into the overall mechanism of the oxidation reaction in two ways that both lead directly to the oxysulfonium ylide **3** that we have previously shown to be the direct precursor of the carbonyl compound.[8] The first of these (Scheme IV) is a concerted, ionic process that

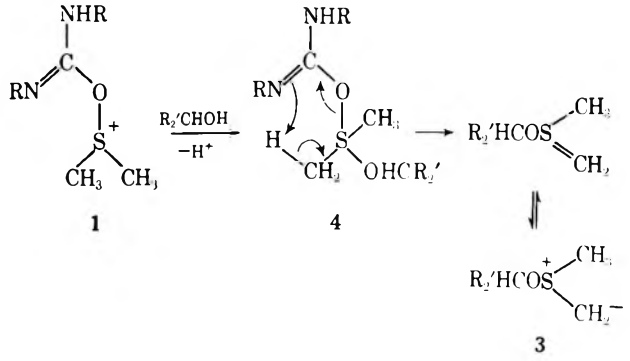
SCHEME IV



is closely related to a portion of the more complex Torssell mechanism (Scheme III).

The second involves addition of the alcohol to the DMSO–DCC adduct **1** with formation of a tetracovalent sulfur intermediate **4** which can then collapse *via* a cyclic process to the oxysulfonium ylide **3** and dicyclohexylurea (Scheme V). A similar tetracovalent

SCHEME V



intermediate was also considered in our earlier work on the reactions of phenols with DMSO and DCC.[4b]

The latter process has the particular advantage that formation of the neutral intermediate **4** removes the positive charge on sulfur that acted as a driving force in the maintenance of very low equilibrium concentrations of the adduct **1** (Scheme II). Loss of this driving force then allows a complete reversal of the electron flow leading, once again, directly to the ylide **3**.

The mechanism which now appears to best represent the overall oxidation reaction is thus a combination of Scheme II with either Scheme IV or V giving the oxysulfonium ylide **3** which can then collapse *via* a cyclic mechanism to the carbonyl compound and dimethyl sulfide as in Scheme I. This does not represent any major deviation from the pathway originally proposed[2a,8] and only differs basically in the manner in which the oxysulfonium proton is abstracted. It is, however, undoubtedly a more correct representation of this useful reaction sequence and will be used in the future in explaining the reactions of DMSO and DCC with other nucleophilic functional groups.

Experimental Section

General Methods.—Thin layer chromatography was conducted using 0.25-mm layers of Merck silica gel GF and products were detected by either their ultraviolet absorption or by spraying with a 5% solution of ammonium molybdate followed by brief heating at 150°. Nuclear magnetic resonance (nmr) spectra were obtained using a Varian A-60 spectrometer and are recorded in parts per million downfield of an internal standard of tetramethylsilane. Mass spectra were obtained at an ionizing voltage of 70 eV using an Atlas CH-4 instrument fitted with a direct inlet system. Infrared spectra were obtained using potassium bromide pellets and a Perkin-Elmer 237 instrument.

Nuclear Magnetic Resonance Studies.—A solution of diisopropylcarbodiimide (0.046 ml, 0.3 mmol) and DMSO-d_6 (0.042 ml, 0.6 mmol) in $CDCl_3$ (0.45 ml) containing 1% tetramethylsilane was placed in a conventional nmr cell and the spectrum was recorded (see text). Dichloroacetic acid (5 μl, 0.06 mmol) was then added and the spectrum was recorded after 1.5 and 10 min. There was no significant change in the spectra except for the appearance of small doublets at 1.10 and 1.47 ppm corresponding to the isopropyl resonances of diisopropylurea and of *N*-dichloroacetyl-*N*,*N*′-diisopropylurea, respectively. Subsequent addition of *p*-nitrobenzyl alcohol (15 mg, 0.1 mmol) led to the rapid formation of *p*-nitrobenzaldehyde that could be detected by tlc using chloroform. Once again, there was no detectable change in the $-SCH_3$ resonances during this phase of the reaction.

***N*-Dichloroacetyl-*N*,*N*′-diisopropylurea.**—Dichloroacetic acid (1.29 g, 10 mmol) and diisopropylcarbodiimide (1.26 g, 10 mmol) were dissolved in dry pyridine (10 ml) and kept overnight at 23°. The brown solution was evaporated to dryness and the residue coevaporated several times with ethanol. The residue was crystallized from ether giving 1.50 g of beige needles that were recrystallized from ether after decolorization with charcoal giving 1.20 g (47%) of colorless needles. An analytical sample had mp 115–116° from isopropyl alcohol: λ_{max}^{MeOH} 208 mμ (ϵ 5800); nmr ($CDCl_3$) 1.25 and 1.42 (d, 1, J = 6 Hz, $CH(CH_3)_2$), 3.97 and 4.51 (quint, 1, J = 6 Hz, $CH(CH_3)_2$), 6.45 ppm (s, 1, $CHCl_2$).

Anal. Calcd for $C_9H_{16}N_2O_2Cl_2$: C, 42.35; H, 6.32; N, 10.97. Found: C, 42.37; H, 6.36; N, 11.07.

Oxidation of Testosterone in DMSO-d_6. A.—Dichloroacetic acid (2 μl, 0.024 mmol) was added to a solution of testosterone (30 mg, 0.1 mmol) and DCC (62 mg, 0.3 mmol) in anhydrous (molecular sieve) DMSO-d_6 (0.1 ml) and benzene (0.2 ml). After 10 min at room temperature the mixture was diluted with anhydrous benzene (0.5 ml) and the crystalline dicyclohexylurea was removed by filtration, washed thoroughly with anhydrous benzene, and dried *in vacuo*. The yield was 30 mg while the theoretical yield for 1 equiv was 22 mg. The infrared spectrum is shown as Figure 1a and the mass spectrum as Figure 2b.

Examination of the filtrate by tlc using chloroform–ethyl acetate (4:1) showed that complete oxidation of the testosterone to androst-4-ene-3,17-dione had occurred. Some further dicyclohexylurea could also be shown to be present in the filtrate.

B. Control Reaction without Alcohol.—A reaction was set up exactly as above except that testosterone was omitted. Separation of dicyclohexylurea was, in this case, slow and incomplete but after 40 min the reaction was diluted with benzene and treated exactly as in A. The yield of dicyclohexylurea was only 5 mg and the mass spectrum of this material is shown as Figure 2c.

Registry No.—**1**, 29474-72-2; *N*-dichloroacetyl-*N*,*N*′-diisopropylurea, 29474-73-3.

Acknowledgment.—Sincere thanks are due to Drs. M. L. Maddox and L. Tokes for their kind assistance with nmr and mass spectrometry, respectively.

Cyclobutyl β-Naphthalenesulfonate Solvolysis. Solvolytic Behavior Study

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The solvolysis rates of cyclobutyl β-naphthalenesulfonate (4-ONas) have been determined in a series of solvents of varying ionizing strength. The correlation of 4-ONas solvolysis rates with those of 2-adamantyl tosylate and pinacoyl brosylate reveals that 4-ONas suffers solvolysis with little nucleophilic assistance by solvent but with considerable anchimeric assistance. The product distributions of 4-ONas in a wide spectrum of solvents corroborates the absence of significant nucleophilic participation by solvent.

Considerable evidence[1,2] has been presented to support the contention that the unusual solvolytic reactivity of cyclopropylcarbinyl derivatives in a wide spectrum of solvents is due to anchimerically assisted ionization (k_Δ)[3,4] and not due to solvent nucleophilic participation (k_s).[3,4]

The relative importance of anchimeric (k_Δ) and solvent (k_s) assistance upon the overall solvolysis rate (k_t) of cyclobutyl derivatives (in the same spectrum of solvents) is less well defined.[5,6] In part, this is due to the lack of a suitable model for evaluating the unassisted ionization rates (k_c)[3,4] of secondary substrates.

Recently, two such models have been proposed, 2-adamantyl tosylate[4] and 3,3-dimethyl-2-butyl (pinacoyl) brosylate.[7] The former is described[4] as a new standard for k_c-type behavior without mention of ion-pair return. The latter is proposed[7] as a new standard for k_c-type behavior unaccompanied by ion-pair return.

This paper reports the results of an investigation where the solvolytic behavior of cyclobutyl β-naphthalenesulfonate, 4-ONas, was compared with that of 2-adamantyl tosylate and pinacoyl brosylate. The data indicate that cyclobutyl β-naphthalenesulfonate suffers solvolysis in a wide range of solvents with little nucleophilic assistance by solvent but with considerable anchimeric assistance.

The first-order rate constants for solvolysis of cyclobutyl β-naphthalenesulfonate in various solvents are summarized in Table I. The reaction progress was followed by titrating the liberated β-naphthalenesulfonic acid. The solvolysis reaction of 4-ONas in 2,2,2-trifluoroethanol was accompanied by 22% internal return isomerization.[8] The apparent first-order rate constants, k_t, in this solvent were computed on the basis of the acid infinity titer and, therefore, are a sum of the rearrangement and the solvolytic rate processes. The fact that the infinity titers in urea buffered and unbuffered reactions were identical supports an internal return isomerization and not a competing acid-catalyzed isomerization.

The product distribution data listed in Table II reveal a marked similarity in all solvents. This result strongly suggests that the same cationic species reacts with solvent in all the investigated solvolysis reactions. The possibility that the reported product distributions

TABLE I

SOLVOLYSIS RATES FOR CYCLOBUTYL β-NAPHTHALENESULFONATE

Solvent	Temp, °C	k_1, 10^5 sec^{-1}	Infinity %
HCO_2H[a]	15	86 ± 1	100
	20	160 ± 5	100
	25	270 ± 8	100
	25	430 ± 7[b]	100
	30	400 ± 10	100
CF_3CH_2OH[c]	25	10 ± 0.2[d]	77
	35	25 ± 0.5	78
	44	58 ± 2[d,e]	78
	50	99 ± 0.5	78
EtOH	50	1.36 ± 0.04	100
	50	1.38 ± 0.05[f]	100
	50	1.38 ± 0.03[g]	100

[a] $\Delta H^\ddagger = 17.2 \pm 0.2$ kcal mol^{-1}; $\Delta S^\ddagger = -13 \pm 1$ eu. [b] Sample 0.045 *M* in HCO_2Li and 0.015 *M* in ester. [c] $\Delta H^\ddagger = 16.9 \pm 0.3$ kcal mol^{-1}; $\Delta S^\ddagger = -20 \pm 1$ eu. [d] Duplicate run. [e] Sample 0.040 *M* in urea and 0.030 *M* in ester. [f] Sample 0.010 *M* in NaN_3 and 0.030 *M* in ester. [g] Sample 0.015 *M* in NaN_3 and 0.030 *M* in ester.

are the result of subsequent isomerization reactions has been ruled out by previously reported product stability studies.[1,2,9]

It is particularly noteworthy that the amount of unrearranged ethanolysis product is no greater than the amount of unrearranged formolysis product. This observation coupled with the very low degree of nucleophilic participation by azide ion[10] argues in favor of a similar low degree of nucleophilic participation by solvent in the ethanolysis reaction of 4-ONas.

The correlation of the cyclobutyl β-naphthalenesulfonate solvolysis rates with those of (a) neophyl tosylate, (b) 2-adamantyl tosylate, and (c) pincaoyl brosylate (*cf.* Figure 1) affords considerable insight concerning the relative importance of the k_Δ and k_s pathways in the solvolysis of 4-ONas. For instance, the good linear free-energy correlation between log *k* for 4-ONas and neophyl tosylate can be interpreted in terms of discrete k_Δ and k_s solvolysis processes[12] and, more importantly, that the k_Δ route is dominant for the solvolysis of 4-ONas in all investigated reactions. This interpretation is true to the extent that log k_t (neophyl tosylate) is a good model for anchimerically assisted solvolyses.[13]

(1) D. D. Roberts, *J. Org. Chem.*, in press.
(2) D. D. Roberts and T. M. Watson, *ibid.*, **35**, 978 (1970).
(3) S. Winstein, E. Albred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).
(4) P. v. R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *J. Amer. Chem. Soc.*, **92**, 2542 (1970).
(5) J. D. Roberts and V. C. Chambers, *ibid.*, **73**, 5034 (1951).
(6) H. C. Brown and G. Ham, *ibid.*, **78**, 2735 (1956).
(7) V. J. Shiner, Jr., R. D. Fisher, and W. Dowd, *ibid.*, **91**, 7748 (1969).
(8) K. L. Servis and J. D. Roberts, *Tetrahedron Lett.*, 1369 (1967).
(9) K. L. Servis and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 3773 (1964).
(10) The incorporation of azide ion, *cf.* Table I, produces almost no rate enhancement for the ethanolysis of 4-ONas. This compares with a threefold rate enhancement observed[11] in the solvolysis of isopropyl tosylate under similar concentration conditions in more strongly ionizing 80% aqueous ethanol.
(11) J. M. Harris, D. J. Raber, R. E. Hall, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 5729 (1970).
(12) I. L. Reich, A. Diaz, and S. Winstein, *ibid.*, **91**, 5635 (1969).
(13) For leading references, see A. F. Diaz and S. Winstein, *ibid.*, **91**, 4300 (1969).

TABLE II

SOLVOLYSIS PRODUCTS FOR CYCLOBUTYL β-NAPHTHALENESULFONATE

Solvent	Buffer			CH_2=$CHCH_2CH_2OS$
EtOH	C_5H_5N	42	53	5
AcOH	NaOAc	44	52	4
AcOH	NH_2CONH_2	45	51	4
HCO_2H[a]	HCO_2Na	45	45	10

[a] Taken from data of K. L. Servis and J. D. Roberts, *J. Amer. Chem. Soc.*, **86**, 3773 (1964).

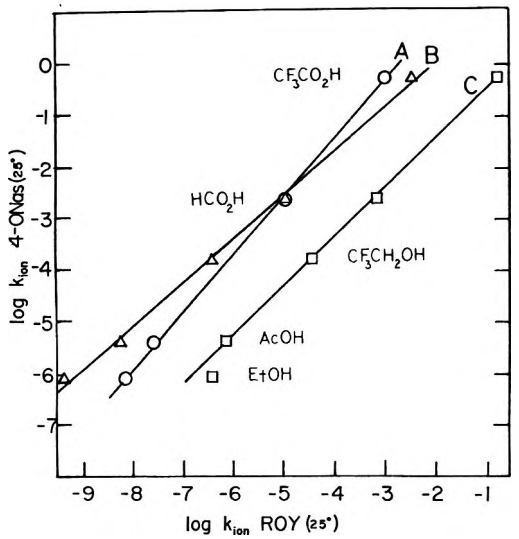

Figure 1.—The linear dependence of log k_{ion} for 4-ONas on log k_{ion} for neophyl tosylate, A; on log k_{ion} for 2-adamantyl tosylate, B; on log k_{ion} for pinacoyl brosylate, C.

It is also seen in Figure 1 that a good linear free-energy correlation exists between log k for **4**-ONas and log k_t for 2-adamantyl tosylate, a model for limiting[4] solvolytic behavior. This observation corroborates the interpretation that the k_s pathway plays only a minor role in the solvolysis reactions of **4**-ONas.

The correlation between log k for **4**-ONas and log k_t for pinacoyl brosylate further reinforces the interpretation that nucleophilic participation by solvent plays a minor role in the solvolysis of **4**-ONas. The accelerated ethanolysis rate of pinacoyl brosylate observed in this correlation is also observed in a similar correlation with log k_t for 2-adamantyl tosylate and lends additional support to the contention that the ethanolysis of **4**-ONas is accompanied by only a low degree of nucleophilic participation by solvent.

Finally, the large magnitude of the k_Δ/k_c data recorded in Table III are cited in support of the speculation that the k_Δ route is, indeed, the dominant pathway while the solvent unassisted pathway, k_c, plays only a minor role in the solvolysis of **4**-ONas. The value of k_c(cyclobutyl)/k_c(2-adamantyl), the solvent invariant rate ratio,[4] was estimated by use of the rate data calculated by Schleyer[14] from steric and conformational considerations and by use of eq 1,[15] where

$$\log \frac{k_c^{4\text{-OTs}}}{k_c^{2\text{-AdOTs}}} \simeq \log \frac{k_{rel}^{4\text{-OTs}}}{k_{rel}^{2\text{-AdOTs}}} = \Delta(\text{steric strain})_{4-2} \quad (1)$$

it is noted that the steric strain term reflects the enhanced steric strain introduced into the cyclobutyl and 2-adamantyl systems by generation of trigonal center typical of a classical cation.

TABLE III

ASSISTED/UNASSISTED RATE RATIOS FOR 4-ONAS, 25°

Solvent	$\frac{k^{4\text{-ONas}}}{k^{2\text{-AdOTs}}}$	k_Δ/k_c[a] 4-ONas
CF_3CO_2H	$10^{2.13}$	$10^{5.23}$
HCO_2H	$10^{2.38}$	$10^{5.48}$
CF_3CH_2OH	$10^{2.40}$	$10^{5.50}$
CH_3CO_2H	$10^{2.61}$	$10^{5.71}$
CH_3CH_2OH	$10^{3.31}$	$10^{6.41}$

[a] Obtained by multiplying $k^{4\text{-OTs}}/k^{2\text{-AdOTs}}$ by $10^{3.1}$, the inherent $k_c^{2\text{-AdOTs}}/k_c^{4\text{-OTs}}$ ratio.

Experimental Section

A Beckman GC-4 chromatographic instrument equipped with a thermal conductivity detector and 8 ft × 0.25 in. columns of 20% diethylene glycol succinate on Chromosorb W, AW-DMCS (45–60 mesh), and 20% 1,2,3-tris(2-cyanoethoxy)propane on Chromosorb W (30–60 mesh) were used for analytical gc work.

Cyclobutyl β-naphthalenesulfonate (4-ONas) resulted when 2-naphthalenesulfonyl chloride (8.0 g, 0.35 mol) was mixed with cyclobutanol (2.16 g, 0.30 mol) and 40 ml of redistilled *sym*-collidine at 0°. After being allowed to stand 16 hr at 0°, the reaction mixture was acidified with cold, 10% aqueous HCl. The precipitated ester was separated on a Büchner funnel, washed three times with cold acid and three times with cold water, and air-dried to yield 7.3 g of crude ester. Recrystallization from 1:1 petroleum ether (bp 30–60°)–ether gave 4.6 g (58%) of white crystals, mp 75–76° (lit.[16] mp 75–76°).

Solvents.—Acetic acid solvent was prepared from 994.9 ml of glacial acetic acid (Matheson Scientific, 99.8%) and 5.1 ml of acetic anhydride. Absolute ethanol was prepared according to the method of Fieser.[17] 2,2,2-Trifluoroethanol (Aldrich Chemical Co.) was redistilled just prior to use. Formic acid solvent was stored several days over boric anhydride, decanted, and distilled from fresh anhydride.

Cyclobutyl β-Naphthalenesulfonate Ethanolysis Products—Cyclobutyl β-naphthalenesulfonate (1.13 g, 5 mmol) was dissolved in sufficient absolute ethanol (containing 10 mmol of dry pyridine) to give 25 ml of solution. After 11 half-lives at 50°, the solution was diluted with 150 ml of water and continuously extracted with ether for 3 days. The ether extract was washed with dilute, aqueous HCl and cold water and dried (Na_2SO_4), and most of the solvent removed by distillation. Analysis by gc revealed, in addition to solvent, the presence of ethyl allylcarbinyl ether, ethyl cyclobutyl ether, and ethyl cyclopropylcarbinyl ether in the ratio 1:8.4:10.6, respectively.

Cyclobutyl β-Naphthalenesulfonate Acetolysis Products.—Cyclobutyl β-naphthalenesulfonate (1.13 g, 5 mmol) was dissolved in sufficient acetic acid solvent (containing 7.5 mmol of NaOAc) to give 25 ml of solution. After 11 half-lives at 50°, the solution was diluted with 150 ml of water and continuously extracted with ether for 2 days. The ether extract was neutralized with $NaHCO_3$, washed with water, and dried (Na_2SO_4)

(14) P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1854, 1856 (1964).

(15) Equation 1 is derived from the relative rate data of ref 14 as follows: log k_{rel}^{x} = log $k^x/k^{6\text{-OTs}}$ = (steric strain)$_x$; log k^y − log $k^{6\text{-OTs}}$ = (steric strain)$_y$; and therefore, log $k_{rel}^{4\text{-OTs}}$ − log $k_{rel}^{2\text{-AdOTs}}$ = Δ(steric strain)$_{4\text{-OTs}-2\text{-AdOTs}}$.

(16) R. A. Sneen, K. M. Lewandoski, I. A. I. Taha, and B. R. Smith, *J. Amer. Chem. Soc.*, **83**, 4843 (1961).

(17) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Health, Boston, Mass., 1957, p 285.

and most of the solvent removed by distillation. Analysis by gc revealed, in addition to solvent, the presence of allylcarbinyl acetate, cyclobutyl acetate, and cyclopropylcarbinyl acetate in the ratio 1:11.0:13.0, respectively. A repeat of this product run where urea was used as the buffer in place of NaOAc gave the same analytical result.

Rate measurements were accomplished by usual techniques.[18] The titrating solutions were, for formolysis, 0.020 *N* sodium acetate in acetic acid and, for ethanolyses and trifluoroethanolyses, 0.020 *N* sodium methoxide in anhydrous methanol. The indicators used were bromphenol blue (in acetic acid), bromthymol blue (in water), and bromphenol blue (in 20% aqueous (EtOH), respectively.

(18) D. D. Roberts, *J. Org. Chem.*, **29**, 294 (1964).

Treatment of Kinetic Data.—The rate constants, k, used in Figure 1 for the acetolysis and 2,2,2-trifluoroethanolysis were calculated according to the following scheme: $k = k_t/(F + F' + F'')$ which was derived from $k_t = Fk + F'k + F''k$ where F = fraction of ion pair yielding solvolysis products, F′ = fraction of ion pair collapsing to allylcarbinyl β-naphthalenesulfonate, and F″ = fraction of ion pair collapsing to cyclopropylcarbinyl β-naphthalenesulfonate. It was assumed that the ratio of total anion collapse to solvent collapse is a constant in a given solvent independent of the detailed distribution of charge in the intermediate. For acetolysis, $k = 34.3 \times 10^{-7}$ sec^{-1} compared to $k_t = 24 \times 10^{-7}$ sec^{-1}. For 2,2,2-trifluoroethanolysis, $k = 16 \times 10^{-5}$ sec^{-1} compared to $k_t = 10 \times 10^{-5}$ sec^{-1}.

Registry No.—4-ONas, 26366-58-5.

Decomposition of *p*-Toluenesulfonylazoalkenes[1]

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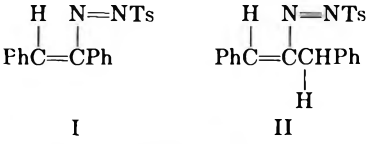
p-Toluenesulfonylazostilbene and 2-*p*-toluenesulfonylazo-1,3-diphenylpropene have been synthesized and decomposed in benzene at 90° and in chloroform at 25°. The results obtained are consistent with a rearrangment of *p*-toluenesulfonylazoenes to the corresponding 2-*p*-toluenesulfonyldiazo compounds and successive protic decomposition. The formation of diphenylacetylene and 1,3-diphenylallene can be ascribed to an internal neutralization of vinyldiazonium ions.

Recently, two papers concerning the reaction of *p*-toluenesulfonylhydrazine with ketones bearing a leaving group on the adjacent carbon have appeared. The first paper[2] reports the formation of diphenylacetylene from benzoin acetate and benzoin benzoate *p*-toluenesulfonylhydrazones with alkali. The proposed mechanism, however, is at variance with experiments previously reported by us.[3,4] The second paper[5] concerns the reaction between *p*-toluenesulfonylhydrazine and α-X ketones *via* *p*-toluenesulfonylazoenes.

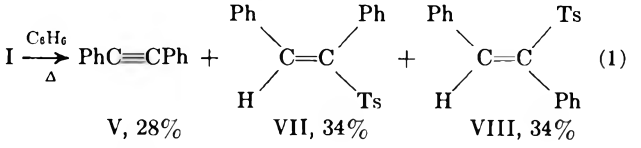
We wish to report here some experiments that confirm the peculiar reactivity of the S–N bond in *p*-toluenesulfonylazoalkenes. In aprotic solvents, treatment of α-acetoxydeoxybenzoin and α-acetoxy-1,3-diphenylpropane-2-one *p*-toluenesulfonylhydrazones with bases gives the corresponding *p*-toluenesulfonylazostilbene (I) and 2-*p*-toluenesulfonylazo-1,3-diphenylpropene (II).



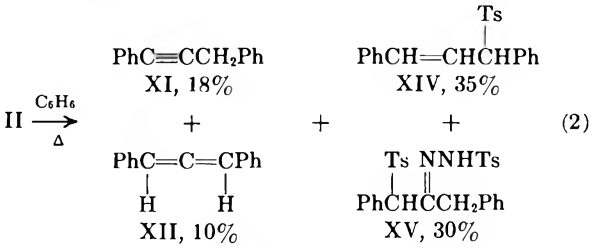
I II

The mechanism of the formation of these compounds is consistent with 1:4 elimination of AcOH by basic treatment.[3,4] The *p*-toluenesulfonylazoenes obtained are yellow compounds which decompose on melting, and their structure has been assigned on the bases of analytical and spectroscopic data (Experimental Section).

The thermal decompositions of I and II in dry benzene at 90° resulted in the evolution of nitrogen and the disappearence of the yellow color of the solution. The mixtures obtained by evaporation of the solvent were separated by column chromatography on silica gel to give the compounds shown in eq 1 and 2.



V, 28% VII, 34% VIII, 34% (1)



XI, 18% XIV, 35% XII, 10% XV, 30% (2)

The same results were obtained if I or II were allowed to stand at room temperature for several hours in $CHCl_3$ solution. The yields of the products were substantially unchanged compared with those from the thermal decomposition in benzene.

In the case of I, the initial yellow color of the solution turned pink during the first hour of reaction, and then this color slowly disappeared while nitrogen was evolved. A pink compound (mp 95° dec from benzene–*n*-pentane) was obtained by removing the chloroform under reduced pressure, in the cold, when the pink color of the solution had become most intense. The analytical values and the physicochemical data suggest that this compound is 1-*p*-toluenesulfonyl-1,2-diphenyl-2-diazoethane (IV). The rearrangement of I to IV has been followed at 25° by scanning the visible spectrum between 350 and 700 mμ every 16 min. The disappearence of the band at 342 mμ of I is consistent with the formation of the band at 500 mμ of IV. The absorption curves for this transformation carried out at 25° in chloroform are shown in Figure 1.

(1) This work was done with financial support of the Italian National Research Council (C.N.R.).

(2) T. Iwadare, I. Adachi, M. Hayashi, A. Matsunaga, and T. Kitai, *Tetrahedron Lett.* No. 51, 4447 (1969).

(3) L. Caglioti, P. Grasselli, F. Morlacchi, and G. Rosini, *Chem. Ind. (London)*, 25 (1968).

(4) L. Caglioti and G. Rosini, *ibid.*, 1093 (1969).

(5) P. Wieland, *Helv. Chim. Acta*, **53**, 171 (1970).

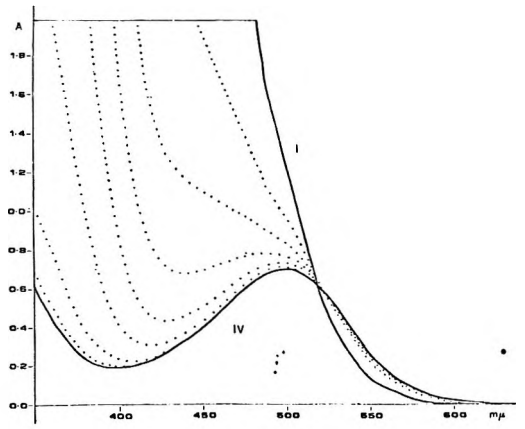
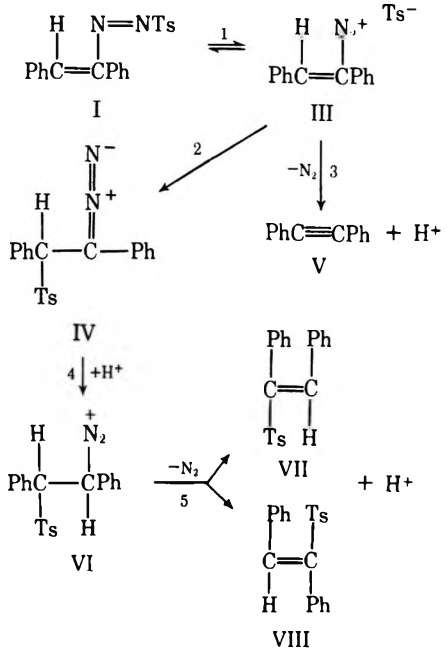


Figure 1.

It was also possible to follow the rearrangement by observing the infrared spectrum. The band at 1630 cm^{-1} characteristic of I disappears, while a strong band at 1960 cm^{-1} ($>C{=}\overset{+}{N}{=}\overset{-}{N}$)[6] characteristic of IV appears. The kinetics of the reaction of IV to form VII and VIII in chloroform were followed by observing the band at 500 mμ, and the results obtained are consistent with a first-order reaction with respect to IV. Duplicate runs at 25° gave $k = 1.5 \times 10^{-5}$ sec^{-1}. On the basis of the above-reported experiments, the course of decomposition of *p*-toluenesulfonylazostilbene (I) can be depicted as in Scheme I.

SCHEME I



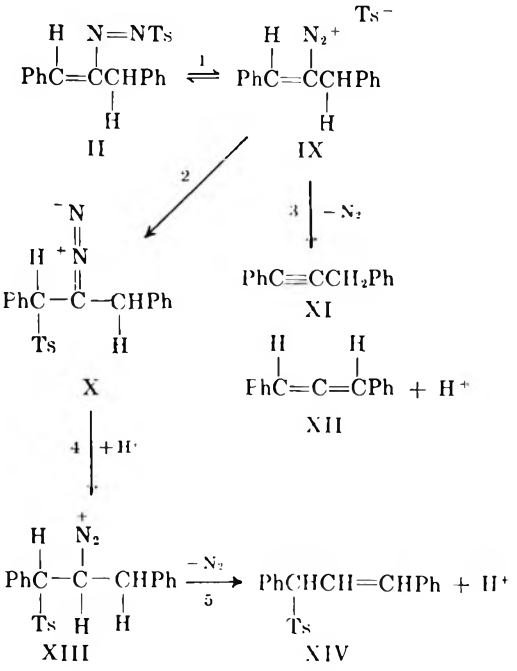
The covalent *p*-toluenesulfonylazoenic form I, by dissociation into diazonium *p*-toluenesulfinate III, rearranges to 1-*p*-toluenesulfonyl-1,2-diphenyl-2-diazoethane (IV), while a fraction of the vinylic diazonium ion undergoes an internal neutralization leading to diphenylacetylene (V), nitrogen, and H^+ ions. The latter protonate the diazo group of IV and, by nitrogen expulsion, *p*-toluenesulfonyl-*cis*-stilbene (VII), *p*-toluenesulfonyl-*trans*-stilbene (VIII), and further H^+ ions are formed.

A carbenic pathway from IV to VII and VIII is also possible; however, pure IV, when dissolved in chloroform at 25°, is stable. If acetic acid is added, a rapid decomposition is observed. This suggests to us that ionic decomposition should largely overwhelm the carbenic pathway. Extensive mechanistic studies of steps 3 and 5 of this reaction have not been carried out, and, consequently, the decomposition of the diazonium ions of III and IV *via* vinyl carbonium ions is, at present, as likely as the one depicted.

The yields in which compounds IV was obtained suggest that the alternative route *via* displacement of the diazonium ion by the *p*-toluenesulfonyl anion leading to the formation of VII and VIII is not possible in this case.

In Scheme II the probable course of the decomposition of 2-*p*-toluenesulfonylazo-1,3-diphenylpropene (II) is depicted.

SCHEME II



During the thermal decomposition of II in dry benzene at 90° and also in chloroform at room temperature, the formation of 1-*p*-toluenesulfonyl-1,3-diphenylpropan-2-one *p*-toluenesulfonylhydrazone (XV) was observed. It is possible to ascribe this to an attack of *p*-toluenesulfinic acid on undecomposed *p*-toluenesulfonylazoalkene to produce a 1:4 addition product.[3]

In addition, the absence of 2-*p*-toluenesulfonyl-1,3-diphenylpropene among the decomposition products seems to exclude nucleophilic displacement on the diazonium ion.

The results reported here are in good agreement with the experiments performed on the decomposition of *p*-toluenesulfonylazocyclohexene in acidic conditions.[7]

Experimental Section

All melting points are uncorrected. Spectra were recorded on Beckman IR-5A, UNICAM SP-800, and MiNiMar Jeolco

(6) P. Yates, B. L. Shapiro, N. Yoda, and J. Fugger, *J. Amer. Chem. Soc.*, **79**, 5756 (1957).

(7) Work is in progress in our laboratory.

spectrometers. Band relative intensity of ir spectra is indicated as follows: vs, very strong; s, strong; m, medium; w, weak; and vw, very weak. Nmr spectra were recorded using TMS as internal standard. Microanalyses were performed using C, H, and N Analyzer Model 185 of Hewlett-Packard Co. Benzoin, 1,3-diphenylpropan-2-one, and *p*-toluenesulfonylhydrazine are commercial materials. Analytical grade solvents were purified by standard methods[8] and distilled through a Vigreux column before use.

α-Acetoxydeoxybenzoin *p*-Toluenesulfonylhydrazone.—α-Acetoxydeoxybenzoin (10 g, 3.9×10^{-2} mol) was dissolved in ethanol and 7.34 g (3.9×10^{-2} mol) of *p*-toluenesulfonylhydrazine added. The solution was allowed to stand until precipitation was judged complete (about 3 days). The crystals were collected, washed with alcohol, and dried (mp 130–132°, yield, 85%). In the infrared spectrum, bands were observed at 3200 (NH), 1720 (>C=O), 1600 (phenyl), and 1160 cm^{-1} (SO_2). Nmr ($CDCl_3$) signals appeared at δ 7.75–6.9 (multiplet, 1 H) for aromatic protons, 6.75 (multiplet, 1 H) for the proton on C bearing acetoxy, 6.20 (singlet, 1 H) for the NH proton, 2.35 (singlet, 3 H) for the methyl of *p*-toluenesulfonyl, and 1.95 (singlet, 3 H) for the methyl of acetoxy.

Anal. Calcd for $C_{23}H_{22}N_2O_4S$: C, 65.39; H, 5.25; N, 6.63. Found: C, 65.20; H, 5.32; N, 6.62.

***p*-Toluenesulfonylazostilbene (I).**—α-Acetoxydeoxybenzoin *p*-toluenesulfonylhydrazone (5.0 g, 1.2×10^{-2} mol) was dissolved in dry benzene and 1.0 g of LiH was added. The mixture was allowed to stand at room temperature with occasional stirring. After about 20 min the yellow solution was filtered and washed several times with water, dried over Na_2SO_4, and filtered, and finally evaporation of benzene gave a yellow product (mp 95° dec, yield 65%). In the infrared spectrum, bands were observed at 3000 (vw), 1630 (w), 1580 (m), 1480 (vw), 1430 (s), 1370 (m), 1335 (vs), 1320 (m), 1300 (m), 1220 (vw), 1180 (m), 1160 (vs), 1130 (w), 1080 (vs), 1065 (s), 1025 (w), 928 (m), 892 (m), 865 (w), 840 (s), 810 (s), 760 (vs), and 735 cm^{-1} (s). Uv (benzene) showed λ_{max} 342 mμ (ε 19,700). Nmr signals ($CDCl_3$) appeared at δ 7.8–6.9 (multiplet, 14 H) for aromatic protons, 6.84 (singlet, 1 H) for the vinylic proton, and 2.34 (singlet, 3 H) for the methyl of *p*-toluenesulfonyl.

Anal. Calcd for $C_{21}H_{16}N_2O_2S$: C, 69.60; H, 5.0; N, 7.73. Found: C, 69.95; H, 5.1; N, 7.63.

α-Acetoxy-1,3-diphenylpropan-2-one *p*-Toluenesulfonylhydrazone.—α-Acetoxy-1,3-diphenylpropan-2-one (10 g, 3.7×10^{-2} mol) was dissolved in ethanol and 6.9 g (3.7×10^{-2} mol) of *p*-toluenesulfonylhydrazine added. The solution was allowed to stand until precipitation of the product was judged complete (about 20 hr). The crystals were collected (mp 132–134°, yield 85%), washed with alcohol, and dried. In the infrared spectrum, bands were observed at 3220 (NH), 1730 (>C=O), 1600 (phenyl), and 1165 cm^{-1} (SO_2). Nmr signals ($CDCl_3$) appeared at δ 8.2–7.0 (multiplet, 14 H) for aromatic protons, 6.70 (multiplet, 1 H) for the proton on C bearing acetoxy, 6.18 (singlet, 1 H) for the NH proton, 3.35 (singlet, 2 H) for benzilic protons, 2.36 (singlet, 3 H) for the methyl of *p*-toluenesulfonyl, and 1.92 (singlet, 3 H) for the methyl of acetoxy.

Anal. Calcd for $C_{24}H_{24}N_2O_4S$: C, 66.04; H, 5.54; N, 6.42. Found: C, 66.24; H, 5.53; N, 6.20.

2-*p*-Toluenesulfonylazo-1,3-diphenylpropene (II).—α-Acetoxy-1,3-diphenylpropan-2-one *p*-toluenesulfonylhydrazone (5.0 g, 1.1×10^{-2} mol) dissolved in 500 ml of ether was placed in a separatory funnel, shaken with an aqueous solution of 10% NaOH, and then washed several times with water. The ethereal solution was dried over Na_2SO_4, the ether evaporated, and a yellow compound was obtained (mp 78–80°; yield 60%). Infrared spectrum bands were observed at 3000 (vw), 1600 (w), 1490 (w), 1450 (w), 1340 (s), 1295 (w), 1165 (s), 1085 (w), 970 (vw), 895 (m), 830 (w), 805 (w), 785 (w), 760 (m), and 695 cm^{-1} (vs) in KBr. Uv (benzene) showed λ_{max} 360 mμ (ε 24,340). Nmr spectrum ($CDCl_3$) showed signals at δ 7.8–6.9 (multiplet, 14 H) for aromatic protons, 6.87 (singlet, 1 H) for the vinylic proton, 3.73 (singlet, 2 H) for allylic protons, and 2.42 (singlet, 3 H) for the methyl of *p*-toluenesulfonyl.

Anal. Calcd for $C_{22}H_{20}N_2O_2S$: C, 70.2; H, 5.36; N, 7.44. Found: C, 69.95; H, 5.45; N, 7.40.

Decomposition of *p*-Toluenesulfonylazostilbene. Route A.—(3.0 g, 8.3×10^{-3} mol) dissolved in 100 ml of dried benzene in a sealed tube was heated in an oil bath at 90°. After a few minutes the benzene solution turned red and this color disappeared rapidly with evolution of nitrogen. The colorless solution was cooled and concentrated under reduced pressure, and then a chromatographic separation was performed on a silica gel column using benzene as eluent. The products obtained were identified as diphenylacetylene (V)[9] (28% yield) and, from the second set of fractions, a 1:1 mixture of the two *p*-toluenesulfonylstilbene isomers (cis and trans). The separation of these was carried out on another silica gel column using [benzene (70%)–cyclohexane (30%)] as eluent.

***p*-Toluenesulfonyl-*cis*-stilbene (VII).**—VII had mp 179–180°. Ir and uv spectra were identical with those of an authentic sample of *p*-toluenesulfonyl-*cis*-stilbene independently prepared.[10] Nmr spectrum ($CDCl_3$) showed signals at δ 8.2 (singlet, 1 H) for the vinylic proton, 7.6–6.7 (multiplet, 14 H) for a romatic protons, and 2.31 (singlet, 3 H) for the methyl of *p*-toluenesulfonyl.

Anal. Calcd for $C_{21}H_{18}O_2S$: C, 75.41; H, 5.38. Found: C, 75.47; H, 5.48.

***p*-Toluenesulfonyl-*trans*-stilbene (VIII).**—VIII had mp 146–148°. Ir and uv spectra were identical with those of an anthentic sample independently prepared.[10] The nmr spectrum ($CDCl_3$) showed signals at δ 7.6–6.5 (multiplet, 15 H) for aromatic protons and a vinylic one and 2.4 (singlet, 3 H) for the methyl of *p*-toluenesulfonyl.

Anal. Calcd for $C_{21}H_{18}O_2S$: C, 75.41; H, 5.38. Found: C, 75.45; H, 5.31.

Decomposition of *p*-Toluenesulfonylazostilbene. Route B. 1-*p*-Toluenesulfonyl-1,2-diphenyl-2-diazoethane (IV).—I (3.0 g, 0.83×10^{-2} mol) was dissolved in dried chloroform (300 ml) in a flask. The solution was allowed to stand at 25° in a thermostat bath and the reaction was followed by the visible spectrum change at the same temperature. During *ca.* 1 hr the formation of a band at 500 mμ was observed. When the absorbance of the band at 500 mμ assigned to IV was most intense, 150 ml of solution was removed from the flask and evaporated under reduced pressure at room temperature. The mixture was purified by crystallization from benzene–pentane and a crystalline product was obtained in a 55% yield (mp 95–96° dec). Uv (cyclohexane) showed λ_{max} 282 mμ (ε 14,880) and uv ($CHCl_3$) λ_{max} 500 mμ (ε 613). Ir spectrum bands were observed at 1960 (vs), 1580 (m), 1490 (m), 1440 (w), 1340 (sh, vw), 1310 (s), 1290 (s), 1165 (sh, m), 1140 (s), 1080 (m), 1030 (vw), 880 (vw), 810 (m), 770 (w), 740 (s), 675 (s), and 645 cm^{-1} (s) in KBr. Nmr signals ($CDCl_3$) appeared at δ 8.0–6.7 (multiplet, 14 H) for aromatic protons, 4.83 (singlet, 1 H) for the benzilic proton, and 2.25 (singlet, 3 H) for the methyl of *p*-toluenesulfonyl.

Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.60; H, 5.0; N, 7.73. Found: C, 69.83; H, 4.92; N, 7.80.

The remaining solution (150 ml) was allowed to stand at 25° until the pink color disappeared, then the solvent was evaporated, and the mixture was taken up in benzene. This solution was placed on a column of silica gel and eluted as for route A. Compounds V, VII, and VIII were obtained in the same yield as in the experiment described above.

Decomposition of 2-*p*-Toluenesulfonyl-1,3-diphenylpropene. Route A.—II (3.0 g, 0.8×10^{-2} mol) in 100 ml of dry benzene was sealed in a tube and treated thermally as described before for I. After 15 min the red solution turned colorless; then it was cooled and evaporated. The mixture was taken up in ether and, on adding cyclohexane, a white precipitate was obtained which was filtered off and crystallized from methanol. The spectroscopic results and microanalytical data led to the assignment to this compound as a *p*-toluenesulfonylhydrazone of 1-*p*-toluenesulfonyl-1,3-diphenylpropan-2-one (XV). The residual solution was again evaporated and taken up in benzene (20%) and cyclohexane (80%) (10 ml), and the mixture was separated by chromatography on a silica gel column with cyclohexane as eluent. Three sets of fractions were collected. The purity of these was checked by tlc on silica gel plates using an uv lamp to reveal the spots. By evaporating the solvent at room temperature with a water aspirator, 1,3-diphenylallene (XII) was obtained in 10% yield from the first set of fractions, and from the second set a pale yellow oil, 1,3-diphenylpropyne (XI), was obtained in about 18% yield. The third set of fractions, after evaporation under the

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same conditions, gave a white product in 35% yield that furnished analytical data consistent with the structure of 1,3-diphenyl-3-*p*-toluenesulfonyl-1-propene (XIV).

1-*p*-Toluenesulfonyl-1,3-diphenylpropen-2-one *p*-Toluenesulfonylhydrazone (XV).—XV had mp 160–162° from methanol. Ir spectrum showed bands at 3200 (s), 3020 (w), 2880 (w), 1640 (w), 1600 (s), 1480 (s), 1400 (vs), 1335 (vs), 1315 (vs), 1230 (m), 1162 (vs), 1130 (vs), 1080 (vs), 1050 (s), 925 (s), 885 (s), 845 (m), 812 (vs), 790 (s), 760 (s), 740 (m), 705 (vs), and 675 cm^{-1} (vs) in KBr. Nmr ($CDCl_3$) signals appeared at δ 8.14 (singlet, 1 H) for the NH proton, 7.85–6.5 (multiplet, 14 H) for aromatic protons, 4.7 (singlet, 1 H) for the proton on C bearing *p*-toluenesulfonyl, 3.38 (singlet, 2 H) for benzilic protons, and 2.34 and 2.18 (two singlets, 6 H) for the two methyls of *p*-toluenesulfonyl.

Anal. Calcd for $C_{29}H_{28}N_2O_4S_2$: C, 65.4; H, 5.30; N, 5.26. Found: C, 64.8; H, 5.12; N, 5.31.

1,3-Diphenylallene (XII).—XII had mp 47–50° from *n*-pentane. Ir and uv spectra were in good agreement with the data reported in the literature.[11] Nmr spectrum (C_6D_6) showed signals at δ 7.5–7.1 (multiplet, 10 H) for aromatic protons and at 6.58 (singlet, 2 H) assigned to allenic protons.

Anal. Calcd for $C_{15}H_{12}$: C, 93.71; H, 6.29; mol wt, 192.25. Found: C, 94.12; H, 6.35; mol wt (mass spectroscopy), 192.

1,3-Diphenylpropyne (XI).—The pale yellow oil distilled at 151–155° (4 mm). Ir and uv spectra were in good agreement with the data reported in the literature.[12] Nmr spectrum (C_6D_6) showed signals at δ 7.5–7.0 (multiplet, 10 H) for aromatic protons and 3.78 (singlet, 2 H) for benzilic protons.

Anal. Calcd for $C_{15}H_{12}$: C, 93.71; H, 6.29; mol wt, 192.25. Found: C, 94.2; H, 6.05; mol wt (mass spectroscopy), 192.

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1,3-Diphenyl-3-*p*-toluenesulfonyl-1-propene (XIV).—XIV had mp 150–153° from CH_2Cl_2–pentane. Ir spectrum showed bands at 3020 (w), 1580 (m), 1480 (m), 1450 (m), 1310 (vs), 1140 (vs), 1080 (m), 1020 (vw), 975 (m), 920 (w), 875 (vw), 810 (m), 780 (m), 750 (vs), 715 (m), and 665 cm^{-1} (m) in KBr. Nmr ($CDCl_3$) signals appeared at δ 7.5–6.9 (multiplet, 14 H) for aromatic protons, 6.42 (multiplet, 2 H) assigned to vinylic protons, 4.65 (multiplet, 1 H) for the proton on C bearing *p*-toluenesulfonyl, and 2.25 (singlet, 3 H) assigned to the methyl of *p*-toluenesulfonyl.

Anal. Calcd for $C_{22}H_{20}O_2S$: C, 75.84; H, 5.79; S, 9.18. Found: C, 75.9; H, 5.65; S, 9.15.

Decomposition of 2-*p*-Toluenesulfonylazo-1,3-diphenylpropene. Route B.—II (3.0 g, 0.8×10^{-3} mol) in 150 ml of dry chloroform was allowed to stand for several hours until the red color of the solution disappeared. After removal of solvent by evaporation under reduced pressure at room temperature, the mixture was treated as indicated for route A. Compounds XI, XII, XIV, and XV were obtained in yields which were not substantially changed from those observed in route A.

Registry No.—I, 29127-96-6; II, 29127-97-7; IV, 29127-98-8; VII, 29119-39-9; VIII, 29119-40-2; XI, 4980-70-5; XII, 19753-98-1; XIV, 29128-01-6; XV, 29128-02-7; α-acetoxydeoxybenzoin *p*-toluenesulfonylhydrazone, 24854-36-2; α-acetoxy-1,3-diphenylpropan-2-one *p*-toluenesulfonylhydrazone, 29128-04-9.

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Meisenheimer-Type Compounds from Heteroaromatic Substrates. The Reaction of Methoxide Ion with 2-Methoxy-3,5-dinitrothiophene[1]

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The formation and isolation of a Meisenheimer-type adduct from 2-methoxy-3,5-dinitrothiophene and methoxide ion are described. Addition of the nucleophile occurs at the 2 position only, to yield the 2,2-dimethoxy-3,5-dinitrothiacyclopentenate ion. The specific rate and, particularly, the equilibrium constant for the formation of this adduct at 25° are larger than the corresponding values for the formation of the adduct between 2,4,6-trinitroanisole and methoxide ion at the same temperature.

Meisenheimer-type adducts formed from nitro-substituted homocyclic aromatic substrates and methoxide ion have been intensively studied.[2] The formation of similar adducts from pyridine and pyrimidine derivatives has been reported[3-8] and compared with the corresponding reactions of homocyclic compounds. We are now considering the behavior of suitable five-membered ring substrates in order to evaluate the role of the ring size and of the heteroatom in the formation of the adducts. Following a preliminary communication,[9] we report detailed results and additional data for the reaction of 2-methoxy-3,5-dinitrothiophene with methoxide ion.

(1) Part XXXVI: Nucleophilic Heteroaromatic Substitution.

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Experimental Section

Materials.—The methanol used for the rate measurements was purified as described;[3] however, since methanol distilled over magnesium methoxide may still contain traces of basic impurities,[10] that used in the experiments carried out in the presence of sodium acetate was redistilled over *p*-nitrobenzoic acid. 2-Methoxy-3,5-dinitrothiophene ($\epsilon_{max} = 0.92 \times 10^4\ M^{-1}\ cm^{-1}$ at 243 nm; $\epsilon_{max} = 1.04 \times 10^4\ M^{-1}\ cm^{-1}$ at 343 nm, in methanol) was prepared by a known procedure[11] and by nitration of 2-methoxy-5-nitrothiophene[12] with 99% nitric acid in acetic anhydride at 0°. Attempts to obtain it by methoxy dechlorination of 2-chloro-3,5-dinitrothiophene were unsuccessful. Other materials used and the analytical and nmr and uv visible spectral

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procedures were as described previously.[3,4] Chemical shifts are approximate to ±0.02 ppm. Ir spectra were determined in KBr disks on a Perkin-Elmer 257 spectrophotometer.

Isolation and Characterization of the Adduct.—2-Methoxy-3,5-dinitrothiophene (40 mg) was dissolved in the least amount of methanol. Nearly 1 equiv of methanolic sodium methoxide (0.7 *M*) was added with a microsyringe. The solution immediately turned reddish purple. The solvent was removed at 10^{-1} Torr at 25°, and the residue, a purple microcrystalline solid, was washed repeatedly with dry benzene and dried to constant weight in order to eliminate any associated solvent.

Anal. Calcd for $C_6H_7N_2NaO_6S$: C, 27.9; H, 2.7; N, 10.85; Na, 8.9. Found:[13] C, 27.8; H, 2.6; N, 10.8; Na, 9.0.

The adduct was characterized through its nmr, ir, and electronic spectra (Results and Discussion). In MeOH solution the adduct was characterized spectrophotometrically as the species obtained when sodium methoxide was added to a solution (2×10^{-5} *M*) of the substrate in methanol. When the concentration of methoxide ion was 4×10^{-4} *M*, the conversion of the substrate into the adduct was complete at 25°. The time required for this was *ca.* 5 min. At concentrations of methoxide greater than 5×10^{-3} *M*, the adduct appeared to be unstable, since the pink color of the solution faded. The rate of fading increased as the concentration of the nucleophile was increased. This behavior was not investigated further; probably the strong excess of the nucleophile is responsible for a ring-opening reaction similar to that undergone by nitrofurans[14] in the presence of strong bases or by 3,4-dinitrofurans with amines.[15]

Rate Measurements. A. Sodium Methoxide as Reagent.—The formation of the adduct is a relatively fast reaction. In order to follow the kinetics at 25°, solutions of the substrate ($2–3 \times 10^{-5}$ *M*) and of sodium methoxide ($3–6 \times 10^{-4}$ *M*) in methanol were placed in the separate compartments of a Y-shaped, thermostated tube. At zero time the solutions were mixed and rapidly poured into a thermostated 1-cm cell. The increase in optical density at 531 nm with time was recorded. The rate data are reported in Table I.

TABLE I

REACTION OF 2-METHOXY-3,5-DINITROTHIOPHENE (MDNT) WITH METHOXIDE ION IN METHANOL SOLUTION AT 25°[a]

[MDNT], $\times 10^5$ *M*	[MeO⁻] $\times 10^4$ *M*	k_{obsd}, $sec^{-1} \times 10^2$	k_{II}, M^{-1} sec^{-1}
2.00	3.93	1.35	34.4
2.00	3.93	1.37	35.0
3.01	5.89	2.16	36.7
3.01	4.71	1.84	38.1
3.01	4.71	1.67	35.5
			Av 36

[a] For comparison, literature data are reported (references quoted in parenthesis) of k_{II} and K_f values for the reaction of trinitroanisole with methanolic methoxide ion at 25°: k_{II} = 7–10 (ref 3), 4 (ref 21), 4.55 [T. Abe, T. Kumai, and H. Arai, *Bull. Chem. Soc. Jap.*, **38**, 1526 (1965)], 16–20 M^{-1} sec^{-1} (ref 24a); K_f = 10,000–20,000 (ref 3), 7700 (ref 21), 2260 [T. Abe, T. Kumai, and H. Arai, *Bull. Chem. Soc. Jap.*, **38**, 1526 (1965)], 17,000 M^{-1} (ref 24a).

B. Sodium Acetate as Reagent.—A small amount of methoxide ions is present when sodium acetate is dissolved in methanol. A 0.1 *M* solution of acetate has a limited buffer capacity so that the interaction of the substrate slightly modifies the methoxide ion concentration. It has been found that the kinetics of formation of the adduct follow a pseudo-first-order law for the first 70–80% of reaction both in the reaction of 2,4,6-trinitroanisole and of 2-methoxy-3,5-dinitrothiophene. Second-order rate constants, k_{II}, were obtained from the equation[3]

$$k_{II} = k_{obsd}/([MeO^-] + K_f^{-1})$$

where k_{obsd} is the experimentally found pseudo-first-order rate constant and K_f is the equilibrium constant for the formation of the adduct. In the experiments using methoxide ion as reagent, the value of K_f^{-1} was negligible compared to that of the concentration of methoxide ion. For the experiments using sodium acetate, K_f was determined as described in the next section. The rate data are reported in Table II.

TABLE II

EQUILIBRIUM AND RATE CONSTANTS FOR THE FORMATION OF THE ADDUCTS IN METHANOLIC SODIUM ACETATE (0.1 *M*) AT 25°

Substrate	Concn, 10^5 *M*	K_f, M^{-1}	k_{obsd}, sec^{-1}	k_{II}, $M^{-1} \times sec^{-1}$
2,4,6-Trinitroanisole[a]	2–3	8.8×10^3	7.75×10^{-4}	4.25
2-Methoxy-3,5-dinitrothiophene[b]	0.9–2.6	4×10^5	9.14×10^{-4}	13

[a] Average value from two determinations; uncertainty is 9% for K_f, 1% for k_{obsd}, and 5% for k_{II}. [b] Average value from two determinations; uncertainty is 8% for K_f, 8% for k_{obsd}, and 7% for k_{II}.

Equilibrium Measurements.—The equilibrium constants

$$K_b = \frac{[AcOH][MeO^-]}{[AcO^-][MeOH]}; \quad K_f = \frac{[adduct]}{[MeO^-][ArOMe]}$$

$$K_{MeOH} = [MeO^-][MeOH_2^+]$$

were combined to give the following relations, neglecting the concentration of $MeOH_2^+$.

$$[MeO^-] = K_b \frac{[AcO^-]}{[AcOH]}; \quad [AcOH] = [MeO^-] + [adduct]$$

Taking the value[16] of K_{MeOH} at 25° as 1.2×10^{-17} and the value[17] of K_a (*i.e.*, K_{MeOH}/K_b) as 2.63×10^{-10} at ionic strength 0.1 *M* and using the experimentally found concentrations of the adduct, the value of K_f was determined (Table II).

Results and Discussion

In deuterated DMSO, 2-methoxy-3,5-dinitrothiophene shows two singlets in the nmr spectrum at τ 1.53 and 5.63 (relative area 1:3). Upon addition of 1 equiv of 5 *M* methanolic sodium methoxide to a 0.5 *M* solution of the substrate, both peaks are shifted upfield. The weaker peak is shifted to τ 2.14 with its intensity almost unchanged; the exact chemical shift of the stronger peak cannot be clearly observed because of an intense signal from methanol in the same region.

A red solid, found to be a 1:1 adduct by elemental analysis, can be isolated from the methanolic solution of the reagents; its nmr spectrum in deuterated DMSO shows two peaks of relative intensity 1:6 at τ 2.13 and 6.71. The former coincides with that observed for the reaction product formed *in situ;* the latter is attributed to two equivalent methoxyl groups. This indicates that the adduct results from a nucleophilic attack by methoxide ion at the carbon atom originally bound to the methoxyl group.

In accordance with a *gem*-dialkoxy structure,[18] the ir spectrum of the solid (2940 w, 1560 m, 1501 s, 1420 s, 1332 s, 1277 vs, 1247 vs, 1216 s, 1173 s, 1127 vs, 1092 sh, 1061 s, 1027 cm^{-1} s) shows strong absorptions in the ketal region[19] (1000–1250 cm^{-1}).

The electronic spectra of a methanolic solution of the isolated adduct and of the product of interaction between the reagents in methanol are identical and display two maxima at 312 nm (ϵ 7.5×10^3 M^{-1} cm^{-1}) and 531

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nm (ϵ 2.3 × 10^4 M^{-1} cm^{-1}), whereas a freshly prepared methanolic solution of the substrate does not absorb in the visible region. This fact might have allowed K_f to be determined directly by recording the change in optical density at equilibrium in solutions containing the same amount of substrate and the nucleophile at different concentrations.[3] However, it was found that at 25° when the concentration of methoxide ion was as low as 4 × 10^{-4} M, and that of the substrate was 2 × 10^{-5} M, the substrate was entirely changed to the corresponding adduct. The value of K_f was then considerably higher than the corresponding value for the adduct of trinitroanisole (K_f = 1–2 × 10^4 M^{-1} at 25°).[3] It was not thought convenient to decrease the concentration of methoxide further, since unavoidable traces of water (10^{-4}–10^{-5} M) and carbon dioxide could hydrolyze and neutralize a certain amount of methoxide ion and introduce inaccuracy in the calculated value of its concentration.

A lower limiting value for K_f at 25° was calculated by assuming that, at the lowest concentration of methoxide, only $^1/_{100}$th of the original amount of 2-methoxy-3,5-dinitrothiophene had not been converted into the adduct. The value obtained (2.7 × 10^5 M^{-1}) is at least ten times higher than the value reported for trinitroanisole.

The kinetics of formation of the adduct were followed at 25° by measuring the increase in optical density at 531 nm; pseudo-first-order kinetics were observed. Both the pseudo-first-order rate constants and the second-order rate constants calculated from them are reported in Table I.

A comparison with the rate constants found for the formation of the adduct of trinitroanisole at the same temperature (7–10 M^{-1} sec^{-1}) shows that the thiophene derivative reacts faster by a factor of about 4 only.

The data obtained in methanolic sodium methoxide indicated that the K_f value was too high for determination. Therefore, it was thought that, because of the high thermodynamic stability of the adduct, the reaction could also be studied in methanolic sodium acetate at a very low concentration of methoxide ion. This salt is solvolyzed in methanol according to the equation

$$AcO^- + MeOH \rightleftharpoons AcOH + MeO^-$$

Since the autoprotolysis constant of methanol[18] and the acidity constant of acetic acid in methanol are known (although literature values for the latter vary somewhat), it is possible to calculate the concentration of the methoxide ion formed from the methanolysis of sodium acetate with reasonable accuracy.

The electronic spectra of 2-methoxy-3,5-dinitrothiophene and 2,4,6-trinitroanisole in methanolic sodium acetate were found to be identical with those observed in methanolic sodium methoxide. In view of the much greater nucleophilicity of the methoxide ion relative to acetate, it is assumed that the acetate ions are responsible for the formation of methoxide ions but do not compete with the latter for the attack on the ring carbon. It must be emphasized that, owing to uncertainties in the pK_a value of acetic acid in methanol, this method provides reliable results in terms of relative rates and equilibrium constants rather than absolute values for each individual substrate.

As to the determination of the constant K_f in the presence of sodium acetate, the concentration of the adduct is conveniently measured spectrophotometrically after the reaction has attained equilibrium (see Experimental Section). The adduct from the thiophene derivative was thus found to be thermodynamically more stable than the adduct of trinitroanisole by a factor of about 40 (Table II). The high K_f value explains why a colorless methanolic solution of 2-methoxy-3,5-dinitrothiophene (10^{-3} M) slowly becomes faintly pink with a small maximum of absorption at 531 nm; the amount of methoxide ion present in pure methanol (*ca.* 10^{-8} M) is sufficient to convert a very small portion of the substrate into the adduct. A noteworthy example of a similar formation of a Meisenheimer-type adduct by reaction of a neutral molecule with the conjugate base of a neutral solvent is the reaction of 4,6-dinitrofuroxan in water; in this case the formation of the adduct is almost complete.[20]

Since the concentrations of the substrates are always much lower than that of the acetate, throughout the reaction the concentration of methoxide ion is expected to remain almost unchanged. Accordingly, the observed kinetics of formation of the adducts follow a pseudo-first-order law up to 70–80% of reaction. The second-order rate constants reported in Table II were obtained by dividing the observed pseudo-first-order rate constants by the methoxide ion concentration which was calculated using Bunnett's[19] value for the pK_a of acetic acid in methanol. The rate constants obtained in acetate solution are comparable to those obtained when methoxide ion was used as reagent. Good agreement is also found for the reactivity ratio between 2-methoxy-3,5-dinitrothiophene and 2,4,6-trinitroanisole.

Several factors have been suggested in order to explain the stability of Meisenheimer-type adducts. First of all, the presence of powerful electron-attracting groups ortho and para to the reaction center is required, so that the negative charge of the nucleophile can be effectively delocalized. Secondly, relief of steric strain and of steric inhibition of resonance with respect to the initial aromatic systems[21] may also contribute to the stability of those adducts characterized by a carbon atom bearing two alkoxy groups and having two adjacent nitro groups. The reality of this effect was shown by X-ray crystallographic analysis of 2,4,6-trinitrophenetole[22] and of its adduct with ethoxide ion.[23] In the adduct, the two nitro groups at the 2 and 6 position were found to be almost coplanar with the ring, whereas in the initial aromatic system they are twisted by 33 and 62° out of the plane and are not allowed to attain full conjugation.

The relatively low reactivity of the alkoxy-bearing position, as compared to that of a hydrogen-bearing position, was interpreted[21] by assuming that the steric crowding in the transition state leading to the 1,1-dialkoxy adduct is larger than in the transition state leading to the 1,3-dialkoxy adduct. This view has been criticized[24] and an alternative explanation has been offered[24b] to this kinetic effect by taking into account

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the influence of multiple alkoxy substitution at a tetrahedral carbon[25] and direct conjugation phenomena between methoxy and nitro substituents.

We may now ask what connection, if any, can be established between the factors affecting the adduct formation in six-membered rings and that in the thiophene system under investigation. In the latter case we have observed a comparable rate of formation and a much higher stability constant relative to the 2,4,6-trinitroanisole system. A comparison in terms of geometrical parameters is not strictly correct since too many changes are involved altogether on passing from one system to another. An important point to keep in mind is that the observed overall stability constant for the five-membered ring system depends not only on the stability of the resulting adduct but also on that of the starting heteroaromatic system. It is likely that the energy content of the thiophene system is higher than that of 2,4,6-trinitroanisole. It is of interest to note that calculations of the localization energy at the 2 position of thiophene,[26] for electrophilic as well as nucleophilic reactions, indicate that the formation of a σ complex at this position is clearly favored with respect to benzene.

There are, however, two points of structural comparison which must be made despite the difficulties of assessment just mentioned. The first point concerns the steric situation of the nitro groups in the thiophene derivative. Because of the lower steric compression between vicinal groups in the five-membered ring and the presence of only one flanking nitro group, the steric factor, *i.e.*, reduced steric inhibition of resonance, cannot account for the stability of the complex. The second point concerns the *relative* change in geometry of the two systems under comparison.

The C(2)–C(1)–C(6) angle in trinitroanisole is almost 120°, while the S–C(2)–C(3) angle of the thiophene derivative should be near to 111.5°.[27] When the C(1) atom in the former compound forms a new bond with methoxide ion, the C(2)–C(1)–C(6) angle in the adduct is forced to a value close to that of a tetrahedral carbon atom (109.5°), and, therefore, a certain amount of strain affects the six-membered ring. As to the adduct of the thiophene derivative, a tetrahedral value can also be expected for the S–C(2)–C(3) angle, but this is much closer to that of the original substrate. It is then to be expected that the formation of the adduct involves less bond strain in the five-membered than in the six-membered ring system.

Although the adduct from 2-methoxy-3,5-dinitrothiophene is thermodynamically stable, it is easily destroyed by a strong excess of nucleophilic reagents (see Experimental Section). Also, in agreement with other workers,[11] we have found that the yield in the methoxy dechlorination of 2-methoxy-3,5-dinitrothiophene is very low. These facts could be reconciled with the generally accepted two-step mechanism of aromatic substitution provided that the intermediate σ complex having a Meisenheimer-type structure in some cases is diverted to a decomposition path other than the one leading to the conventional substitution product.

Registry No.—MDNT, 27357-00-2; methoxide ion, 3315-60-4; 2,2-dimethoxy-3,5-dinitrothiacyclopentenate ion, 29152-91-8.

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Substituent Effects in the Reaction of Sodium 4-Nitrophenoxide with 2-Bromoacetanilides

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The kinetics of the reaction of sodium 4-nitrophenoxide with ten 3′- and 4′-substituted 2-bromoacetanilides in 2-methoxyethanol solvent have been examined at 45.3, 55.3, and 65.3°. Second-order kinetics were found, and the rate constants were fit to a Hammett-type equation using van Bekkum, Verkade, and Wepster normal σ values to yield a ρ value of $+0.65 \pm 0.02$, independent of temperature. The amide link is transmitting substituent effects relatively efficiently in this process. Apparently normal activation parameters were encountered.

The transmission of activation effects through acyl links in compounds of the type XCH_nCOZY from Y to a reactive site X adjacent to the carbonyl group has been little studied; Z is taken to be an atom with an unshared electron pair, nitrogen in the present case. A considerable body of information relates the effect of a change at X with reactivity or equilibria at the carbonyl group or at atom Z; examples are of the pK_a's of substituted amino acids[3] and phenylacetic acids,[4] the infrared frequencies of substituted anilides,[5] the hydrolysis reactions of phenylacetates,[6] as well as many other reactions which could be cited. On the other hand, when this work was begun virtually no work had been reported which dealt with transmission of effects from Y to X; for example, no measurements of pK_B of substituted glycine anilides have been reported. It is clear that

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transmission of activation effects through amide, ester, and thio ester chains to the carbon atom adjacent to the carbonyl group has important biochemical implications.

A Hammett-type correlation is used in our studies. A suitably substituted group of compounds XCH_n-COZAr is prepared and the reaction at X is studied kinetically (or an equilibrium constant could be determined); if a Hammett type correlation is obtained, ρ is taken as a measure of the transmission efficiency.[7-9] We have studied the elimination of hydrogen bromide from N-alkyl- (or aryl-) N'-(β-bromopropionyl)ureas[10a] and the addition of ethanol to substituted acrylanilides catalyzed by sodium hydroxide;[10b] in both these examples the transmission efficiency of the amide group appeared to be high. The ^{19}F nmr of trifluoroacetanilides were found to correlate with σ^+, but the σ value was found to be low (0.06).[11] Professor Menger has measured the pK_a's of some anilides of *p*-hydroxybenzoic acid and found a low ρ value (0.06).[12] The present work extends the previous studies to the displacement reaction of sodium 4-nitrophenoxide on 2-bromoacetanilides in what seems to be a simple SN2-type reaction.

Ten variously substituted 2-bromoacetanilides were prepared by reaction of the aniline with bromoacetyl bromide. The products had the expected infrared and nmr spectra; proper analyses were obtained for new compounds. After some experimentation the reaction of the bromoacetanilides with sodium 4-nitrophenoxide in 2-methoxyethanol was chosen for kinetic study (eq 1).

$$BrCH_2CONHAr + 4\text{-}O_2NC_6H_4O^- \longrightarrow 4\text{-}O_2NC_6H_4OCH_2CONHAr + Br^- \quad (1)$$

The reaction proceeded at a reasonable rate at accessible temperatures and could be followed conveniently by monitoring the nitrophenoxide band at 405 nm; neither the bromoanilides nor the product nitrophenoxyacetanilides absorbed appreciably at this wavelength with the exception of 3′-nitro-2-bromoacetanilide. A rearrangement reaction of the product ether to 4-nitrophenylarylamines did provide a potential interference problem, but the rearrangement was not encountered in appreciable amounts in kinetic runs. The product ethers were synthesized by reaction of the nitrophenoxide with bromoacetanilides at slightly higher concentrations than those used in the kinetic runs. Microanalyses, infrared spectra, and nmr spectra were consistent with the expected products.

The synthetic scale reactions leading to the product ethers were subjected to thin layer chromatography periodically to detect the presence of additional components. In most instances only starting materials and final products were detectable. In a few preparations an additional yellow component was noted toward the end of the reaction; this component was shown to be 4-nitrodiphenylamine in the reaction of bromoacetanilide with 4-nitrophenoxide by comparison of the

$$O_2NC_6H_4OCH_2CONHAr \longrightarrow O_2NC_6H_4NHAr + \text{"}OCH_2CO\text{"}$$

isolated component with an authentic sample using melting point, infrared spectra, and nmr spectra. The yellow product from 2,4′-dibromoacetanilide and 4-nitrophenoxide was shown to be 4-nitro-4′-bromodiphenylamine by melting point, nmr spectra, and infrared spectra. The rearrangement of this class of compounds was reported in low yield by Smiles[13] using hot aqueous sodium hydroxide with glycolic acid as the other product. In our hands reaction of the 2-(4-nitrophenoxy)-acetanilides with bases such as carbonate in aqueous methanol led to 50–70% yields of the diphenylamine upon reflux for a few hours. No effort was made to achieve higher yields, though the reaction seems to be an easy entry into the diphenylamine series.

The kinetics of the reactions were followed under pseudo-first-order conditions; the nitrophenoxide (typically 10^{-4} *M*) concentration was followed in the presence of excess bromoacetanilide (typically 10^{-2}–10^{-3} *M*). The reactions gave good first-order plots to 80–90% completion. The data were analyzed by least-squares analysis. The average deviation from the best straight line was 0.8–1.1%. Agreement of rate constants between identical runs was within 1–3%. Three runs were made for each reported rate constant at 55.3° using at least two different sets of solutions and two runs were made for each reported rate constant at 45.3 and 35.3°. Reported points are an average of the runs conducted. Carbon dioxide caused some difficulties, and it was necessary to work under a nitrogen atmosphere with anhydrous solvents and reagents. The data supporting the second-order character of the reaction are in Table I. The reaction of 4-nitrophenoxide with 2-bromoacetanilide in methoxyethanol at 55.28 ± 0.04° gave a second-order rate constant of $2.33 \pm 0.04 \times 10^{-3}\ M^{-1}\ sec^{-1}$ for anilide concentrations varying from 2.98 to 8.71×10^{-2} *M* with the initial nitrophenoxide concentration 5.77×10^{-4} *M*.

TABLE I

RATE OF REACTION OF *p*-NITROPHENOXIDE WITH α-BROMOACETANILIDE IN 2-METHOXYETHANOL (55.28°)

$[RBr],^a$ $M \times 10^2$	$[ArO^-],^b$ $M \times 10^4$	$10^3k_1,^c$ min^{-1}	$10^3k_2,^c$ $M^{-1}\ sec^{-1}$
5.767	5.78	8.34 ± 0.09[d]	2.41
5.767	5.78	8.06 ± 0.06	2.33
5.822	5.77	8.27 ± 0.03	2.37
8.714	5.77	11.95 ± 0.06	2.29
8.714	5.77	12.06 ± 0.08	2.31
2.981	5.77	4.13 ± 0.03	2.31
2.981	5.77	4.09 ± 0.04	2.28
			Av 2.33 ± 0.04

[a] Concentration of α-bromoacetanilide. [b] Concentration of sodium *p*-nitrophenoxide. [c] k_1 is the pseudo-first-order rate constant; k_2 is the second-order rate constant. [d] Error is the average deviation from best straight line for the particular kinetic run. An average of 15 points were used per line.

Each of the compounds studied has an NH which might act as an acid toward the base 4-nitrophenoxide yielding product through an α-lactam intermediate. Rate determinations were carried out in the presence of

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TABLE II

REACTION OF SODIUM *p*-NITROPHENOXIDE WITH SUBSTITUTED α-BROMOACETANILIDES IN 2-METHOXYETHANOL

Substituent	Registry no.	10^2k_2, M^{-1} sec^{-1} 45.27°	55.27°	65.25°	σ^n
4-OCH_3	29182-87-4	0.747 ± 0.016[a,b]	1.97 ± 0.03	4.99 ± 0.05	−0.175[c]
4-CH_3	5343-65-7	0.786 ± 0.013	2.03 ± 0.05	5.22 ± 0.04	−0.129
H	5326-87-4	0.884 ± 0.017	2.33 ± 0.04	6.08 ± 0.02	0
4-Cl	5343-64-6	1.41 ± 0.03	3.57 ± 0.02	9.19 ± 0.02	0.238
4-Br	5439-13-4	1.42 ± 0.01	3.71 ± 0.06	9.54 ± 0.06	0.265
4-$CO_2C_2H_5$	29182-92-1	1.78 ± 0.01	4.52 ± 0.02	11.4 ± 0.05	0.385
4-$COCH_3$	29182-93-2	1.98 ± 0.02	5.17 ± 0.05	13.0 ± 0.13	0.502
3-OCH_3	29182-94-3		2.45 ± 0.02		0.076
4-SO_2CH_3	29182-95-4		7.39 ± 0.07		0.686
3-NO_2	29182-96-5		6.38 ± 0.07		0.710
4-H-NCH_3[d]	29182-97-6		3.20 ± 0.01		
ρ[e]		0.66 ± 0.02	0.65 ± 0.03[f]	0.64 ± 0.01	
r		0.995	0.991	0.998	

[a] Errors quoted are average of average deviation from best straight line for individual runs. [b] Initial concentrations except for 4-SO_2CH_3 and 3-NO_2 were [RBr] ~ 5.8 × 10^{-2} *M*; [ArO$^-$] ~ 5.8 × 10^{-4} *M*. For 3-NO_2 and 4-SO_2CH_3, initial concentrations were [RBr] ~ 3 × 10^{-2} *M*; [ArO$^-$] ~ 5.8 × 10^{-4} *M*. [c] Reference 14. [d] Compound is *N*-methyl-α-bromoacetanilide. [e] Computed by the method of Jaffé, ref 8. Errors in ρ are Jaffé's *S* or $S\rho$. [f] ρ value computed from some substituents as used at 45 and 65° is +0.65 ± 0.02, r = 0.997.

2,6-lutidine (at five times the concentration of the 4-nitrophenoxide) using 4′-methyl-2-bromoacetanilide in excess; in the presence of the lutidine the second-order rate constant was 2.13 × 10^{-3} M^{-1} sec^{-1}; in its absence the rate constant was 2.03 × 10^{-3} M^{-1} sec^{-1}. The small difference (within the combined experimental error) between the two runs is taken as insignificant. In addition the *N*-methyl derivative of 2-bromoacetanilide was prepared and its rate of reaction compared to that of the NH compound. With essentially identical concentrations of materials the rate constant of the *N*-methyl compound was 3.20 × 10^{-3} M^{-1} sec^{-1}; that for the NH compound was 2.33 × 10^{-3} M^{-1} sec^{-1}. Certainly the NH is not required to attain the rates observed. If an α-lactam were an intermediate, its formation could be rate determining, in which case base catalysis should be observed. Alternatively, reaction of the α-lactam with 4-nitrophenoxide could be rate determining, in which case second-order kinetics with the phenoxide should have been observed. In addition, the reaction of the *N*-methyl compound should have been substantially slower than the N–H compound in either case if an α-lactam is required. The NH is probably inactive in the displacement reactions studied.

The rate constants for individual compounds at three temperatures are shown in Table II at 45.3, 55.3, and 65.3°. Ten compounds were measured at 55.3° and seven at the other two temperatures. All compounds were measured at essentially the same concentration except those with 4-CH_3SO_2 and 3-O_2N substituents. These substituents caused a sufficiently fast reaction that the concentrations of the anilides had to be reduced by a factor of about two to be measurable with the techniques used on the other compounds.

The rate constants were fit to variations of the Hammett equation. As was the case with other displacement reactions, the fit to the original Hammett equation was not good with compounds having negative σ substituents. For example, 4-methyl and 4-methoxy have essentially identical rate constants. For this reason we chose to use the "normal" substituent constants of van Bekkum, Verkade, and Wepster;[14] with these substituent constants the ρ value obtained at 55.3° was 0.65 ± 0.03. The correlation coefficient[8] was 0.991. The ρ for 65.3 and 45.3° was 0.64 ± 0.02 and 0.66 ± 0.03, respectively, with the corresponding correlation coefficients 0.998 and 0.995. The difference in correlation coefficients between the 55.3° and other runs is due almost exclusively to the inclusion of values for 4-CH_3SO_2- and 3-O_2N-bearing compounds at this temperature; these compounds deviate from the best straight line (in opposite directions) far more than any other compounds.

It is clear that the substituent effect from the aromatic ring is being transmitted to the reaction site, presumably through the amide bonds. How efficient the transmission is calculated to be depends upon the models chosen for comparison. The reaction of benzyl chloride with potassium iodide in acetone at 20° has a ρ of +0.786 (correlation coefficient 0.86).[8] The reaction of benzyl chloride with trimethylamine in benzene has dramatic curvature[15] and did not appear to be a useful comparison point. Alternatively, the reactions of phenacyl halides might be used as comparison data. Essentially two classes of ρ values for phenacyl halides with nucleophiles exist. With nucleophiles such as methoxide[16] and cyanide[17] high ρ values (2.82 for methoxide in methanol at 25°) are obtained. With methoxide it has proven possible to isolate epoxide compounds, suggesting substantial carbonyl participation. With other less basic nucleophiles substantially lower ρ values have been observed in reactions with phenacyl halides. For example, the reaction of aniline with substituted phenacyl halides in 90% ethanol at 30.5° shows that a ρ value of 0.597 (correlation coefficient 0.98)[18] is found. This and the rate constants immediately following have been recalculated using σ^n values;[14] better agreement is noted than with standard σ values. Phenacyl bromide with pyridine in acetone at 20° shows a ρ value of 0.54.[19] Triphenylphosphine with phenacyl

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(18) J. W. Baker, *J. Chem. Soc.*, 1128 (1933).

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bromides in nitromethane at 34.9° has a ρ value of 0.45.[20] The reaction of 2,6-dimethyl-4-thiopyrone with phenacyl in benzene at 25.4° has a ρ of 0.95.[21] If one assumes that the values for benzyl chloride with potassium iodide and the lower range of ρ values (0.3–0.9) for phenacyl halide displacement reactions are valid comparison points, then the 0.65 ρ value reported here indicates reasonably efficient transmission of activation effects.

The energy parameters of activation for each compound are shown in Table III. The entropy of activation values reported are apparently normal for reactions of an ion with a neutral molecule.[22] The absence of an appreciable temperature coefficient for ρ over the temperature range studied is worth noting; the ρ values at 65, 55, and 45° were identical within experimental error.

TABLE III

ACTIVATION PARAMETERS FOR REACTION OF *p*-NITROPHENOXIDE WITH SUBSTITUTED α-BROMOACETANILIDES

Substituent	ΔE_a, kcal/mol	$\Delta S^{\pm}$, eu
4-OCH_3	20.4	−11.0[a]
4-CH_3	20.3	−11.1
H	20.7	−9.7
4-Cl	20.1	−10.6
4-Br	20.5	−9.5
4-$CO_2C_2H_5$	19.9	−10.7
4-$COCH_3$	20.2	−9.6

[a] Entropy of activation calculated at 55° from the equation $\Delta S^{\pm} = 4.577 \log A - 60.716$.

It is interesting that the two kinetic measurements reported have given appreciable transmission of substituent effects through the amide bond; ρ for the addition of ethanol to acrylanilides[11] was +1.77, and ρ for the displacement reactions reported here was +0.65. On the other hand the measurement of pK values by Donohue, Scott, and Menger[13] and the ^{19}F chemical shifts for trifluoroacetanilides[12] both gave values of less than 0.1. The data thus far reported indicate a transition state effect rather than major contributions from bround state differences, but more must be done to substantiate this possibility.

The mechanism of transmission is not established by work to date. A predominant inductive effect appears untenable because of the σ^n dependence which was observed, but either a resonance-type effect or a more generalized polar effect (polarizability) could account for the effects found to date.

Experimental Section

Bromoacetyl bromide was purchased from Aldrich Chemical Co. 4-Methylthioaniline was purchased from Matheson Coleman and Bell. Sodium 4-nitrophenoxide dihydrate obtained from Eastman Organic Chemicals was dried in an Abderhalden-type vacuum drying apparatus. 2-Methoxyethanol obtained from Matheson Coleman and Bell was stored over Linde Molecular Sieve 5A and anhydrous sodium carbonate and then distilled twice under a nitrogen atmosphere. The distillate boiling between 121.0 and 122.0° uncorr was collected.

A Perkin-Elmer Model 137 sodium chloride spectrophotometer was used to obtain all infrared spectra. A Varian Associates Model A60 analytical nmr spectrometer was used to obtain nmr spectra. A Thomas-Hoover capillary melting point apparatus was used to determine melting points; melting points were corrected.

Preparation of 2-Bromoacetanilide and Its Derivatives.—A solution of 0.10 mol of aniline in 100 ml of benzene was added to a stirred solution of 0.05 mol of bromoacetyl bromide in 200 ml of benzene at room temperature. A mild exothermic reaction occurred and aniline hydrobromide precipitated out of the reaction mixture. The reaction mixture was stirred for 30 min, and the benzene was removed using a rotary evaporator. The residue was dissolved in 95% ethanol, and the solution was acidified by the addition of 3 N sulfuric acid.[23a] Addition of water to the solution induced crystallization. The product[23b] was collected by suction filtration and washed with water. The filtrate possessed lachrymatory properties. The product was recrystallized from ethanol–water using decolorizing carbon. The yield of 2-bromoacetanilide obtained after two crystallizations from benzene was 43%.

The following derivatives of 2-bromoacetanilide were prepared using the above procedure: unsubstituted, mp 134.0–135.0° (reported 130–131°,[24] 129–130°[25]); 3′-OCH_3, mp 98.5–99.5° (unreported[26]); 4′-OCH_3, mp 130.5–131.5° (unreported[26]); N-CH_3, mp 46.5–47.5° (reported 46.8–47.3°,[27] 69°[28]); 4′-CH_3, mp 165.5–167° (reported 164°[29]); 4′-chloro, mp 155.5–156.5° (reported 153–155°,[30] 161°[31]); and 4′-bromo, mp 169–170° (reported 168–169°[30]). The following derivatives of 2-bromoacetanilide were prepared as above except that the acetone was used for the reaction solvent: 4′-$CO_2C_2H_5$, mp 121.0–121.5° (unreported[26]); 4′-$COCH_3$, mp 158–159° (reported 157°[32]); 4′-SO_2CH_3, mp 185.5–186.5° (reported 134°[33]), a correct analysis was obtained for this compound,[26] and 3′-NO_2, mp 124.5–125.5° (unreported[24]). All of the anilines required for the syntheses, except the 4-SO_2CH_3, were commercially available.

Conversion of 4-Methylthioaniline to 4-Methylsulfonylaniline.—4-Methylthioaniline was acetylated quantitatively with acetic anhydride using the procedure described by Fieser[34] for the acetylation of aniline. The melting point was 128–129.5°, lit. mp 128°[35] and 130.5°.[36]

4′-Methylthioacetanilide was treated with 30% H_2O_2 according to the procedure described by Yagupol'skii and Marenets,[37] with the only modifications that the quantity of each reagent used was increased fivefold and that the time of reaction was reduced to 5–10 min. The reaction was monitored by thin layer chromatography. The product isolated using the original 2-hr heating period appeared as two components on a thin layer chromatogram, and the nmr spectrum of the product mixture indicated that 4′-methylsulfonylacetanilide composed only about 10% of the mixture. The major product was isolated as canary yellow needles, mp 139–140.5°; infrared and nmr spectra were consistent with its identification as 4-nitrophenyl methyl sulfone (lit. mp 141°[38] and 142.5°[39]). The desired product crystallized

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(23) (a) The use of concentrated HCl in the preparation of 2,4′-dibromoacetanilide caused a significant conversion of the desired 2-bromo product into the 2-chloro product detected by nmr spectra in the products. (b) When 3-nitro- and 4-carboethoxyaniline were used, the corresponding aniline salts were isolated along with the desired 2-bromoacetanilide product. The mixed product was extracted with ether to free the desired product from the aniline salt. The presence of the aniline salt could be recognized by examining the infrared spectrum of the product.

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(36) L. Gattermann, *Justus Liebigs Ann. Chem.*, **393**, 215 (1912).

(37) L. M Yagupol'skii and M. S. Marents, *Zh. Obshch. Khim.*, **27**, 1935 (1957); *Chem. Abstr.*, **52**, 2781 (1958).

(38) T. Zinke and S. Lenhardt, *Justus Liebigs Ann. Chem.*, **400**, 2 (1913).

(39) W. R. Waldron and E. E. Reid, *J. Amer. Chem. Soc.*, **45**, 2402 (1923).

from an ethanol–water mixture in 60% yield, mp 187.5–189° (lit. mp 183°[40] and 185–186°[37]). The nmr and infrared spectra were consistent with this structure.

4′-Methylsulfonylacetanilide was hydrolyzed to 4-methylsulfonylaniline with dilute HCl. A 78% yield was obtained after crystallization from chloroform, mp 139–140.5° (lit. 133°[41] and 134–135°[37]). Infrared and nmr spectra were consistent with the postulated structure and different from the major product in the paragraph above.

Preparation of Substituted 2-(4-Nitrophenoxy)acetanilides.—A reaction mixture of 500 mg of substituted 2-bromoacetanilide, a 10% mole excess of anhydrous sodium 4-nitrophenoxide, and 10 ml of anhydrous 2-methoxyethanol was heated at 55°. The progress of the reaction was monitored by thin layer chromatography on silica gel with chloroform or chloroform with 2–5% ethanol as the eluent. The reaction time varied from 1 to 30 hr depending upon the 2-bromoacetanilide derivative used. Approximately 200 ml of water was added to the reaction mixture to precipitate the product. The ether was collected by vacuum filtration, washed with water, and air-dried. Thin layer chromatography on silica gel plates indicated that only one product was formed in the faster reactions, but that in the slower reactions the product contained about 1% of a yellow impurity, which was identified as a substituted 4-nitrodiphenylamine.

The product was purified by dissolving it in acetone, filtering off any solid materials, then adding 2–3 vol of benzene, and distilling off the acetone. If the product did not crystallize from the benzene solution, the product was crystallized from a mixture of benzene and cyclohexane. The yellow impurity was generally eliminated as a contaminant by crystallization. The yellow impurity could be eliminated easily by column chromatography on silica gel with benzene elution. The yellow impurity moved rapidly through the column in contrast to the slow-moving product.

The following ring-substituted 2-(4-nitrophenoxy)acetanilides were prepared: unsubstituted, mp 170.5–171.5° (reported 170–171,[42] 170,[43] 172°[26]); 3′-NO_2, mp 180.5–181.5° (reported 177–180°[44]); 4′-OCH_3, mp 179–180° (unreported[26]); 3′-OCH_3, mp 121–122° (unreported[26]); 4′-CH_3, mp 128–128.5° (unreported[26]); 4′-Cl, mp 181–181.5° (unreported[26]); 4′-Br, mp 167–168° (unreported[26]); 4′-$CO_2C_2H_5$, mp 189.5–190.5° (unreported[26]); 4′-$COCH_3$, mp 193.5–194.5° (unreported[26]); 4′-SO_2CH_3, mp 202.5–203.5° (unreported[26]); and N-CH_3, 116.5–117.5° (unreported[26]). Nmr and infrared spectra were obtained for all compounds and were consistent with the postulated structures.

Conversion of 2-Bromoacetanilide to 2-(4-Nitrophenoxy)-acetanilide and 4-Nitrodiphenylamine.—A mixture of 1.00 g (4.67 mmol) of 2-bromoacetanilide, 0.83 g (5.15 mmol) of sodium 4-nitrophenoxide, and 20 ml of 2-methoxyethanol was heated at 55–60° for 64 hr. The progress of the reaction was followed by thin layer chromatography using silica gel adsorbent and chloroform as the eluent. The solvent was removed from the reaction mixture with a Büchi rotary evaporator, and the residue was extracted twice with 200-ml portions of hot benzene. The residue obtained upon removing the benzene with a rotary evaporator was chromatographed on a silica gel column using benzene as the eluent. A yellow compound moved rapidly through the column and yielded 15 mg of 4-nitrodiphenylamine after crystallization from cyclohexane. The assignment of structure was based upon comparison of spectra and a mixture melting point with a commercially available authentic sample.

Sodium carbonate was added to a 1:1 water–ethanol solution of 2-(4-nitrophenoxy)acetanilide, and the mixture was refluxed until thin layer chromatography on silica gel coated microscope slides with chloroform as the eluent indicated complete consumption of the 2-(4-nitrophenoxy)acetanilide present. The yield of 4-nitrodiphenylamine, mp and mmp 135–136°, was 40%. In similar fashion were prepared 4-nitro-4′-bromodiphenylamine, mp 161.5–162.5°, and 4-nitro-4′-chlorodiphenylamine, mp 180–181°.

Determination of the Rate Constants.—The reaction flask was a single-neck, flat-bottom boiling flask modified by the addition of a 8 × 90 mm side tube. The side tube bore a rubber septum. The reaction flask was equipped with a cold finger condenser by means of a straight type adapter with a hose connector to serve as a nitrogen inlet.

Stock solutions of anhydrous sodium 4-nitrophenoxide and 2-bromoacetanilide in dry 2-methoxyethanol were prepared in 50-ml volumetric flasks at room temperature and were stored in a cool, dark cabinet. The quantities of sodium 4-nitrophenoxide and 2-bromoacetanilide used were known by direct weighing.

The 2-bromoacetanilide stock solution (20 ml) was syringed into the reaction flask equipped with a magnetic stirrer and a static atmosphere of nitrogen. The solution was thermally equilibrated with the water bath for approximately 20 min, and then 0.5–1 ml of the sodium 4-nitrophenoxide stock solution was syringed into the reaction flask. The volumes were accurate within 2%.

The initial sample was removed immediately after addition of the sodium 4-nitrophenoxide solution and subsequent samples were taken at constant time intervals of 7.5–30.0 min, depending upon the rate of the reaction. The reaction time, during which 12–22 samples were taken, varied from 1.5 to 10.5 hr.

Samples were removed and quenched by cooling to room temperature. The absorbance of the sodium 4-nitrophenoxide in the sample solution was immediately measured in 1-mm cells using a Beckman Model DB spectrophotometer with a Model SRL Sargent recorder attached; the appropriate 2-bromoacetanilide stock solution was used as the reference solution. The absorbance of the sample solution was measured at 405 nm and varied between an initial value of about 1.050 to a final value of about 0.100 absorbance units, when further measurements were discontinued.

Good straight lines were obtained with a pseudo-first-order plot of the data up to 80–90% reaction. The data were analyzed using a least-squares fitting to the best straight line. The slope error was usually between 0.40 and 0.90%

Registry No.—Sodium *p*-nitrophenoxide, 824-78-2.

(40) R. Child and S. Smiles, *J. Chem. Soc.*, 2699 (1926).
(41) W. R. Waldron and E. E. Reid, *J. Amer. Chem. Soc.*, **45**, 2405 (1923).
(42) C. Kym, *J. Prakt. Chem.*, **55** [2], 113 (1897).
(43) T. H. Minton and H. Stephen, *J. Chem. Soc.*, **121**, 1594 (1922); *Chem. Abstr.*, **39**, 2207 (1945).
(44) C. E. Sparks, U. S. Patent 2,361,327 (1944).

Proportions of Isomers from Mononitration of 2,4,6-Trinitrobiphenyl (Picrylbenzene)

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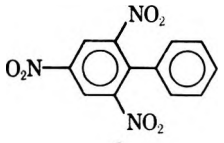
The nitration of 2,4,6-trinitrobiphenyl (picrylbenzene) has been studied in order to ascertain the directive influence of the 2,4,6-trinitrophenyl (picryl) group in electrophilic aromatic substitution. The expected isomers, *o*-, *m*-, and *p*-nitropicrylbenzene, were synthesized by Ullmann reactions and were shown to be stable under the nitrating conditions used (solvent acetic acid at 100°, 2 hr). In an apparently novel use of Varian A-60 nmr spectrophotometer output, the composition of the nitration product was determined by matching its integrator curve with those of synthetic mixtures having nearly the same composition. The result was 8.0 ± 0.4% *o*-, 30.0 ± 0.8% *m*-, and 62.0 ± 0.8% *p*-nitropicrylbenzene.

The nitration of 2,4,6-trinitrobiphenyl (**1**) is of interest in connection with the theory of orientation in



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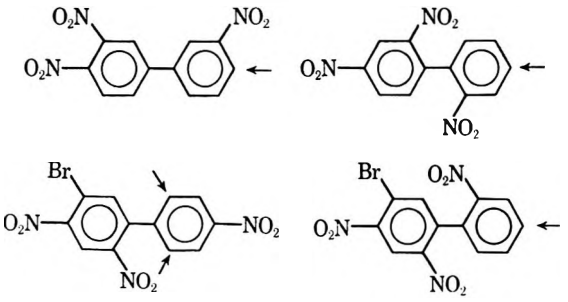
electrophilic aromatic substitution, especially as it relates to biphenyl and its derivatives. Nitration of biphenyl[2] and its derivatives usually takes place chiefly ortho and para to a substituent phenyl group, even when the substituent phenyl group is loaded with meta-directing or electron-withdrawing substituents.[2b,3] The examples of Chart I are particularly relevant.[3l,o]

CHART I

PREFERRED POSITIONS FOR NITRATION OF SOME TRINITROBIPHENYLS



Exceptions occur when the ortho–para-directing influence of a chlorine or bromine is in competition with that of a nitrophenyl group, as in the examples of Chart II.[3i,k,m,n]

The orientation effect in biphenyl is attributable to effective delocalization of charge into the substituent phenyl group in the intermediate carbonium ion resulting from ortho or para attack[4] (Chart III). Such delocalization is not possible when the attack is in a position meta to the phenyl group. The examples of Chart II, however, indicate that a chlorine or bromine is better able to delocalize charge (by electron release) than a nitrophenyl group.

CHART II

PREFERRED POSITIONS FOR NITRATION SHOWING THAT THE ORTHO–PARA DIRECTING INFLUENCE OF A HALOGEN EXCEEDS THAT OF A NITROPHENYL GROUP

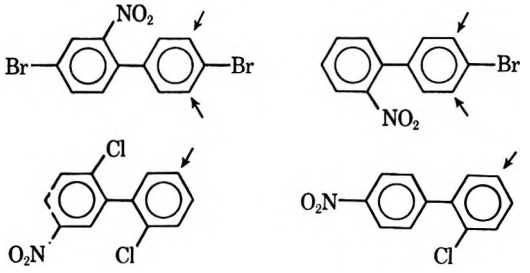
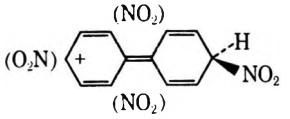


CHART III

ONE OF THE PRINCIPAL RESONANCE FORMS OF THE CARBONIUM ION INTERMEDIATE FOR NITRATION OF BIPHENYL (OR 2,4,6-TRINITROBIPHENYL), ILLUSTRATED WITH PARA ATTACK



The 2,4,6-trinitrophenyl, or "picryl," group occupies an extreme position among modified phenyl substituents, in that the nitro group is one of the most strongly deactivating and meta-directing substituents;[5] and in 2,4,6-trinitrobiphenyl the three nitro groups are so positioned that every resonance form of the intermediate making use of the trinitrophenyl group for charge delocalization has a strongly electron-withdrawing nitro group on the carbon bearing the positive charge (Chart III). The intermediates necessary for substitution ortho and para to the picryl group might be expected to be no more stabilized, therefore, than the intermediate for meta substitution, and the picryl group might be without any orienting influence on the

(1) On leave from St. Xavier's College, Ahmedabad, India.

(2) (a) M. J. S. Dewar, T. Mole, D. S. Urch, and E. W. T. Warford, *J. Chem. Soc.*, 3573, 3576 (1956); (b) Y. Mizuno and O. Simamura, *ibid.*, 3875 (1958).

(3) (a) H. C. Gull and E. E. Turner, *ibid.*, 491 (1929); (b) W. Blakey and H. A. Scarborough, *ibid.*, 3000 (1927); (c) W. S. M. Grieve and D. H. Hey, *ibid.*, 968 (1933); (d) H. G. Dennett and E. E. Turner, *ibid.*, 476 (1926); (e) R. J. W. Le Fèvre and E. E. Turner, *ibid.*, 2041 (1926); (f) R. J. W. Le Fèvre, D. D. Moir, and E. E. Turner, *ibid.*, 2330 (1927); (g) R. J. W. Le Fèvre and E. E. Turner, *ibid.*, 1158 (1930); (h) E. E. J. Marler and E. E. Turner, *ibid.*, 1359 (1931); (i) F. R. Shaw and E. E. Turner, *ibid.*, 285, 509 (1932); (j) E. E. J. Marler and E. E. Turner, *ibid.*, 266 (1937); (k) F. H. Case, *J. Amer. Chem. Soc.*, **64**, 1848 (1942); (l) F. H. Case, *ibid.*, **64**, 2225 (1942); (m) F. H. Case and R. U. Schock, Jr., *ibid.*, **65**, 2086 (1943); (n) F. H. Case, *ibid.*, **65**, 2137 (1943); (o) F. H. Case, *ibid.*, **67**, 116 (1945).

(4) (a) J. D. Roberts, R. A. Clement, and J. J. Drysdale, *ibid.*, **73**, 2181 (1951); (b) B. M. Wepster, *Recl. Trav. Chim. Pays-Bas*, **75**, 1473 (1956).

(5) P. B. D. de la Mare and J. H. Ridd, "Aromatic Substitution," Academic Press, New York, N. Y., 1959, pp 83–88.

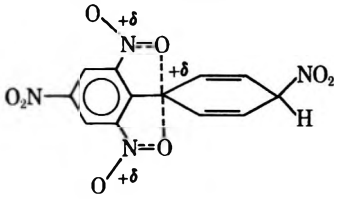
meta and para positions.[6] This would be an *electronic inhibition of resonance.*

Steric inhibition of resonance is also a possibility with the picryl group. Steric interference between the two ortho nitro groups and the two ortho hydrogens on the other ring might prevent the two rings from assuming the coplanar arrangement necessary for resonance stabilization of the intermediates for ortho and para substitution (Chart III). If this were completely effective, and excluding other possible effects, the picryl group would be without orienting influence on the meta and para positions, and statistics would lead one to expect twice as much meta as para product.[7]

It might be argued also that the picryl group should be a meta-directing group. With resonance inhibited electronically and sterically, there remains what may be a strong electron-withdrawing inductive effect, like that of the CF_3 group, which appears to be nearly 100% meta directing.[5,8] The effect of this would be to destabilize the intermediate carbonium ion resulting from ortho and para attack, thus favoring meta substitution.

The pathway pictured in Chart III requires that the benzene rings be coplanar for effective resonance participation by the picryl group. With the benzene rings in orthogonal planes, however, the ortho nitro group oxygens of the picryl substituent might be able to stabilize the carbonium ion resulting from ortho or para nitration through delocalization of charge by a field effect as shown in Chart IV. This pathway and the

CHART IV
ALTERNATIVE PATHWAY FOR NITRATION OF 2,4,6-TRINITROBIPHENYL



one pictured in Chart III are mutually exclusive because of the requirement that the rings be orthogonal for one and coplanar for the other. Thus, it might be possible to assess the relative importance of these two mutually exclusive pathways by experiments with a 2,6-disubstituted picrylbenzene, in which the pathway of Chart III is sterically excluded. Such experiments are planned for this laboratory, for which the results reported here are a necessary preliminary.

Nitration of 2,4,6-Trinitrobiphenyl.—Because of uncertainty regarding the orienting influence of the picryl group in electrophilic aromatic substitution, and as a first step in a possible assessment of the relative importance of the influences pictured in Charts III and IV, we have studied the nitration of 2,4,6-trinitrobiphenyl. In connection with this study, the three expected mononitration products, namely, 2,2′,4,6-, 2,3′,4,6-, and 2,4,4′,6-tetranitrobiphenyl, were synthesized by Ullmann reactions[9] between picryl chloride and the appropriate iodonitrobenzene in order to have standards for use in analysis of the reaction product.

Nitration of 2,4,6-trinitrobiphenyl was carried out with an excess of nitric acid in acetic acid in a boiling water bath for 2 hr. By pouring the reaction mixture into water, the product was obtained in quantitative yield. In separate experiments, each of the three expected mononitration products was treated similarly and was recovered almost quantitatively, unchanged in melting point and appearance.

By fractional crystallization of the nitration product, 2,4,4′,6-tetranitrobiphenyl (para substitution product) was isolated in crude form in about 30% yield and in pure form in 15% yield. Despite several changes of solvent, however, fractional crystallization did not yield another pure isomer.

Attempts to separate or to analyze the nitration mixture by thin layer and column chromatography were unsuccessful. The mass spectra of the three isomers were obtained but were too complex and too poorly reproducible to be of value in quantitative analysis of the mixture. The infrared spectra of the three isomers were simple, and the differences among them appeared to be too small to make them useful for quantitative analysis. Ultraviolet absorption spectroscopy appeared unpromising as a method of analysis, in view of its proven inadequacy with the nitroethylbenzenes.[10] The nmr spectra of the three isomers, however, presented in part in Chart IV, showed significant marked differences and seemed to offer a means of quantitative analysis of the nitration mixture.

Nmr Analysis.—The nmr spectra of the nitration product and of the three isomeric tetranitrobiphenyls (or nitropicrylbenzenes) were obtained in dimethyl sulfoxide (DMSO) as solvent. The solvent signal provided a convenient upfield reference point. Integrator tracings were run in the aromatic region, 410–290 cps downfield from the DMSO singlet.

All samples showed an isolated singlet displaced about 402 cps from the DMSO singlet, which accounted for precisely one-third of the total radiant energy absorption in the aromatic region.[11] Clearly, this singlet arose from the two isolated protons on the triply nitrated ring.

The remaining two-thirds of the absorption occurred almost wholly in the region 290–360 cps downfield from the DMSO singlet. This part of the spectrum for each isomer and the nitration product is shown in Figure 1.

The integrator curves in this region were converted to digital form and normalized. Base lines and upper limits (horizontal portions of the integrator tracings) were carefully selected, with attention being paid to mutual alignment of the several curves both horizontally and vertically. The height of each curve above the base line was measured at integral values of the chemical shift with respect to the DMSO singlet.[12]

(6) Steric hindrance, of course, would be expected to reduce the amount of ortho substitution. A pathway favoring ortho substitution, involving an initial association of the nitrating agent with the nitro groups, followed by an intramolecular rearrangement, cannot be ruled out however (ref 5, p 76).

(7) Reference 5, footnote, p 163.

(8) F. Swarts, *Bull. Acad. Roy. Belg.* 389 (1920); *Chem. Abstr.*, **16**, 2316 (1922).

(9) F. Ullmann and J. Bielecke, *Ber.*, **34**, 2174 (1901).

(10) L. Fey and J. Rusu, *Rev. Roum. Chim.*, **14**, 613 (1969); *Anal. Abstr.*, **19**, 1410 (1970).

(11) The spectra were run several times and with different samples, and the position of this singlet for the ortho isomer was always found to be about 1 cps further downfield than that for the other isomers and the nitration mixture, showing greater deshielding by the proximal nitro group.

(12) An illuminated magnifier having a millimeter scale at the field of vision was used, of a type used by philatelists and like the "Flash-O-Lens" magnifiers available from most laboratory supply houses.

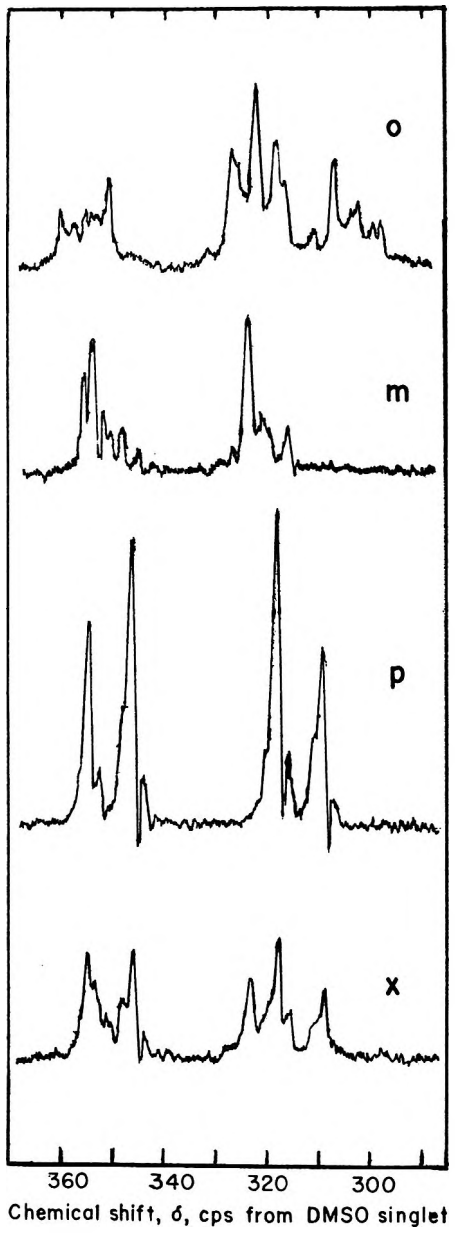


Figure 1.—Portions of the proton nmr spectra of *o*-, *m*-, and *p*-nitropicrylbenzene and of the product (x) of nitration of 2,4,6-trinitrobiphenyl.

Each height was converted to a percentage of the total absorption for the four protons involved. Typical normalized integrator curves are presented in Figure 2.

The curve for the nitration product, labeled "x," clearly shows the presence of the ortho isomer, especially in the region around 340 cps where the ortho curve has a plateau at 25% and the meta and para curves are nearly coincident at about 50% of the total absorption. An estimate of the percentage of ortho isomer could readily be made by using the data at several integral values of the chemical shift in this region. With this estimate of the ortho percentage, the percentages of meta and para isomers could be estimated by using the data in the regions around 350 and 320 cps, where the meta and para curves differ widely.

One set of data thus gave the result 8.2 ± 1.0% ortho, 25.0 ± 5.0% meta, and 66.8 ± 5.0% para. Another set of data obtained on a different day with different samples gave the result 8.4 ± 1.2% ortho, 26.0 ± 5.0% meta, and 65.6 ± 5.0% para. It did not

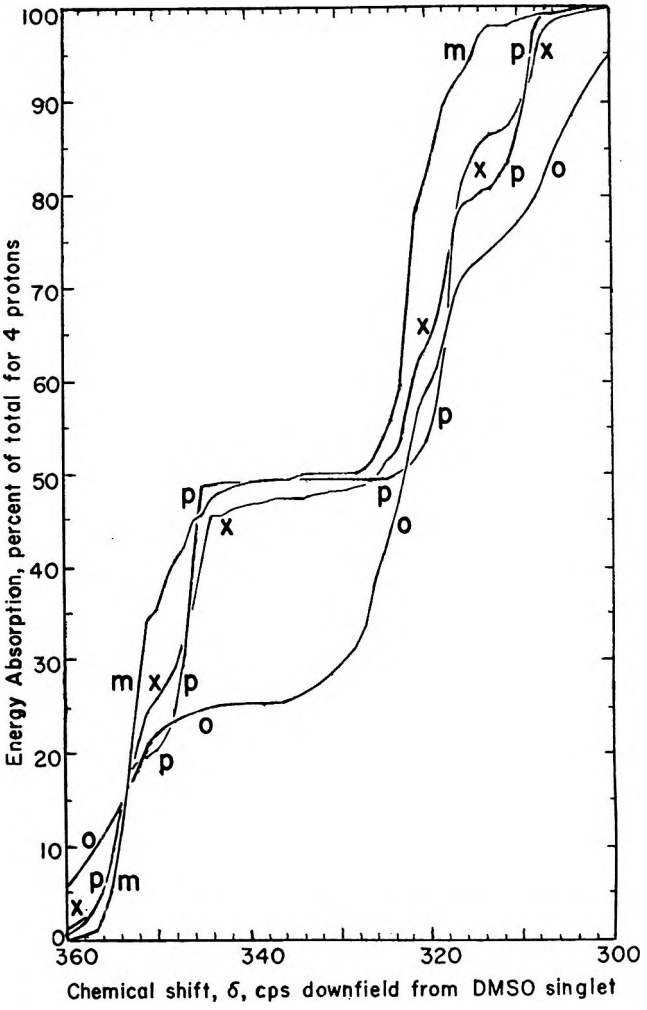


Figure 2.—Normalized A-60 nmr spectrophotometer integrator curves for four protons of *o*-, *m*-, and *p*-nitropicrylbenzene and of the product (x) of nitration of 2,4,6-trinitrobiphenyl.

seem to be possible to reduce the uncertainty in the meta and para percentages below 5% by using the data in this way.

Accordingly, synthetic mixtures of the three isomers were prepared having nearly the composition indicated by the above treatment of the data. Integrator curves for two such mixtures that seem to bracket the nitration product mixture are shown in Table I. They are designated "W" and "Y," while the nitration product is "X."[13] The differences, Y − X, are mostly smaller than the differences W − X, and a statistical treatment based on 20 points (those designated by footnote *f*), for which the difference between W and Y is large, led to the result that the difference between X and Y is 41 ± 12% of the difference between W and Y. Interpolating to this extent between the compositions of the mixtures W and Y gives a mixture "Z" that is 8.0 ± 0.4% ortho, 30.0 ± 0.8% meta, and 62.0 ± 0.8% para. The uncertainty in the meta and para percentages is taken as 12% of the difference (6.8) in the percentages of meta isomer in the mixtures W and Y, while the uncertainty in the ortho percentage is made conservatively so as to include both synthetic mixtures and in recognition of the fact that it was not possible to reproduce an in-

(13) The product curve "X" in Table I is an average of two curves obtained on different days. After alignment of the two sets of data so as to make the algebraic sum of the differences between them equal to zero, the average of the differences between the 68 points for each curve was 0.39.

TABLE I
COMPARISON OF NORMALIZED INTEGRATOR CURVES

δ,[a] cps	Diff W − X	Syn mix[b] W	Product[c] X	Syn mix[d] Y	Diff Y − X	Calcd diff[e] Z − X	δ,[a] cps	Diff W − X	Syn mix[b] W	Product[c] X	Syn mix[d] Y	Diff Y − X	Calcd diff[e] Z − X
365	0.4	0.4	0.0	0.0	0.0	0.2	330	−0.2	48.0	48.2	48.3	0.1	0.0
4	0.2	0.4	0.2	0.2	0.0	0.1	9	−0.3	48.2	48.5	48.6	0.1	−0.1
3	0.0	0.4	0.4	0.4	0.0	0.0	8	−0.2	48.5	48.7	49.0	0.3	0.1
2	0.0	0.6	0.6	0.6	0.0	0.0	7	−0.2	49.0	49.2	49.5	0.3	0.1
1	−0.1	0.8	0.9	0.8	−0.1	−0.1	6	−0.2	49.7	49.9	50.4	0.5	0.2
360	−0.2	0.9	1.1	1.0	−0.1	−0.1	5	−0.6	50.5	51.1	51.6	0.5	0.1
9	−0.7	1.2	1.9	1.6	−0.3	−0.5	4	−0.6	51.4	52.0	52.8	0.8[f]	0.2
8	−0.5	1.7	2.2	2.2	0.0	−0.2	3	−1.0	52.8	53.8	54.7	0.9[f]	0.1
7	−0.5	2.3	2.8	3.2	0.4	0.0	2	−1.9	55.5	57.4	58.4	1.0[f]	−0.2
6	−0.4	4.0	4.4	5.1	0.7	0.3	1	−2.5	59.3	61.8	62.4	0.6[f]	−0.6
5	−0.2	7.2	7.4	8.2	0.8	0.4	320	−2.5	61.5	64.0	64.3	0.3	−0.9
4	0.3	12.3	12.0	13.6	1.6	1.1	9	−3.2	63.5	66.7	66.8	0.1	−1.2
3	−0.6	17.1	17.7	18.8	1.1[f]	0.4	8	−3.1	67.7	70.8	70.6	−0.2	−2.0
2	−1.1	20.4	21.5	22.4	0.9[f]	0.1	7	−3.4	72.2	75.6	75.6	0.0	−1.4
1	−1.6	22.9	24.5	24.8	0.3[f]	−0.5	6	−2.3	79.1	81.4	82.6	1.2[f]	−0.2
350	−1.4	24.5	25.9	26.5	0.6[f]	−0.2	5	−1.2	82.1	83.3	84.8	1.5[f]	0.4
9	−1.6	26.1	27.7	28.3	0.6[f]	−0.3	4	−2.4	83.1	85.5	86.8	1.3[f]	−0.2
8	−0.8	28.4	29.2	29.6	0.4[f]	−0.1	3	−1.5	84.9	86.4	87.4	1.0[f]	0.0
7	−1.9	30.3	32.2	32.8	0.6[f]	−0.4	2	−1.5	85.3	86.8	87.9	1.1[f]	0.0
6	−0.9	35.3	36.2	37.2	1.0[f]	0.2	1	−1.0	86.3	87.3	88.5	1.2[f]	0.3
5	−0.7	40.4	41.1	42.0	0.9[f]	0.3	310	−1.4	87.5	88.9	90.1	1.2[f]	0.1
4	0.4	45.8	45.4	46.0	0.6	0.5	9	−0.7	90.3	91.0	92.4	1.4	0.6
3	0.8	46.3	45.5	46.2	0.7	0.7	8	0.0	93.9	93.9	95.6	1.7	1.0
2	0.4	46.6	46.2	46.9	0.7	0.6	7	0.2	97.8	97.6	98.3	0.7	0.5
1	0.3	46.8	46.5	47.1	0.6	0.5	6	0.3	98.7	98.4	98.7	0.3	0.3
340	0.3	47.2	46.9	47.2	0.3	0.3	5	0.5	99.3	98.8	99.1	0.3	0.4
9	0.2	47.2	47.0	47.2	0.2	0.2	4	0.6	99.7	99.1	99.4	0.3	0.4
8	0.0	47.2	47.2	47.4	0.2	0.1	3	0.5	99.8	99.3	99.5	0.2	0.3
7	−0.1	47.3	47.4	47.4	0.0	0.0	2	0.4	99.9	99.5	99.6	0.1	0.2
6	−0.3	47.3	47.6	47.6	0.0	−0.1	1	0.2	99.9	99.7	99.7	0.0	0.1
5	−0.2	47.4	47.6	47.8	0.2	0.0	300	0.3	100.1	99.9	99.9	0.0	0.1
4	−0.2	47.4	47.6	47.9	0.3	0.1	9	0.2	100.1	99.9	99.9	0.0	0.1
3	−0.4	47.4	47.8	48.1	0.3	0.0	8	0.5	100.5	100.0	100.0	0.0	0.2
2	−0.3	47.6	47.9	48.2	0.3	0.0						Algebraic sum	2.5
1	−0.3	47.8	48.1	48.2	0.1	−0.1						Average |Z − X|	0.31

[a] Chemical shift downfield from DMSO singlet. [b] Synthetic mixture: 8.4% *o*-, 25.9% *m*-, and 65.7% *p*-nitropicrylbenzene. [c] Product of nitration of picrylbenzene (2,4,6-trinitrobiphenyl). [d] Synthetic mixture: 7.8% *o*-, 32.7% *m*-, and 59.5% *p*-nitropicrylbenzene. [e] Differences between product curve X and a curve Z, calculated by interpolation between curves W and Y, for a mixture: 8.0% *o*-, 30.0% *m*-, and 62.0% *p*-nitropicrylbenzene. [f] These points were used in estimation of the composition of X (see text).

tegrator curve with an average deviation for 68 points of less than about 0.4 percentage units.[13]

An integrator curve Z could be calculated, then, for a mixture that is 8.0% *o*-, 30.0% *m*-, and 62.0% *p*-nitropicrylbenzene. The differences between that curve and the curve X for the nitration product are tabulated. Their average is 0.31 percentage units and their algebraic sum is nearly zero (Table I).

It is concluded, therefore, that the nitration of 2,4,6-trinitrobiphenyl gives a mixture that is very nearly 8.0% *o*-, 30.0% *m*-, and 62.0% *p*-nitropicrylbenzene. The $^1/_2$ meta/para ratio, 0.24, leads to classification of the picryl group as an ortho–para-directing substituent, while the very low $^1/_2$ ortho/para ratio, 0.065 indicates much steric hindrance to substitution in an ortho position.

Experimental Section

Melting points were obtained with a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Picryl chloride was prepared by the reaction of pyridine picrate with phosphorus oxychloride according to published procedures,[14] mp 78–81° (lit.[15] 79–81°).

Iodobenzene was prepared by iodination of benzene in the presence of nitric acid,[15] bp 184–186° (lit.[16] 184–186°).

***o*-, *m*-, and *p*-Iodonitrobenzene** were prepared by diazotization of the corresponding nitroaniline and addition of the filtered diazonium salt solution to a 25% solution of potassium iodide in water.[16] The *p*-iodonitrobenzene solidified and was collected by filtration with suction and purified by crystallization from 95% ethanol. The *o*- and *m*-iodonitrobenzene separated as oils and were purified by distillation with steam: ortho, mp 52–54° (lit.[17] 54°); meta, mp 37–38° (lit.[17] 38.5°); para, mp 171–173° (lit.[17] 174°).

2,4,6-Trinitrobiphenyl was prepared by an Ullmann reaction between picryl chloride and iodobenzene[3a] (for procedure, see below). It crystallized from 95% ethanol as golden brown leaflets, mp 128–130° (lit.[3a] mp 130°).

***o*-, *m*-, and *p*-Nitropicrylbenzene** were prepared by Ullmann reactions between picryl chloride and the corresponding iodonitrobenzene. Several different procedures were used in efforts to maximize yields. The copper bronze was described as "Pale-gold Extra Brilliant No. 7," manufactured by U. S. Bronze Powders, Inc., Flemington, N. J. It was used with and without activation with iodine in acetone.[18] A typical procedure was as

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(18) Reference 16, p 192.

follows. In a 125-ml erlenmeyer flask were placed 0.5 g of picryl chloride, 0.5 g of *o*-iodonitrobenzene, and 0.5 ml of dimethylformamide (DMF). The solids were brought into solution by slight heating and mixed thoroughly by swirling, and 0.45 g of copper bronze (untreated) was added and mixed in thoroughly by swirling. The brilliant golden fluid mixture was heated at 160° (oil bath) for 30 min, whereupon it became dull brown and lost its fluidity. It was cooled slightly, 10 ml of 95% ethanol was added, and the mixture was boiled for several minutes with stirring with a glass rod and then filtered. This extraction with hot ethanol was repeated twice. The combined filtrates were treated with decolorizing carbon and filtered. Upon cooling, the filtrate deposited crystals. The solvent was removed by decantation; the crystals were washed with 95% ethanol and recrystallized from 95% ethanol, yield 75 mg (11%), golden yellow prisms, mp 172–173°. When the mother liquor from recrystallization of the product from a previous run was used for the recrystallization, the yield was 106 mg (16%). The reaction was also carried out without DMF with similar results.

In variations of the foregoing procedure, reactions were carried out successfully with as much as 10 g of each halide in as much as 100 ml of DMF with reflux times of 7–8 hr and also without DMF at temperatures as high as 190°. In some large-scale runs without DMF, however, and at the higher temperatures, violent decomposition occurred. The compounds are described in Table II.

TABLE II

NITROPICRYLBENZENES

	Isomer		
	Ortho	Meta	Para
Appearance	Golden yellow prisms	Yellow microneedles	Tan microcrystalline powder
Mp, °C	172–173	181–184	200–202
Solvent for crystn	95% EtOH	95% EtOH	Aqueous HOAc
Anal. Found:[a]			
C, %	43.29	43.19	43.34
H, %	1.77	1.96	1.80
N, %	14.74	14.68	15.38

[a] *Anal.* Calcd for $C_{12}H_6N_4O_8$: C, 43.11; H, 1.80; N, 16.76.

Nitration of 2,4,6-Trinitrobiphenyl.—A mixture of 10 g of 2,4,6-trinitrobiphenyl, 100 ml of glacial acetic acid, and 100 ml of 90% ("fuming") nitric acid (density 1.5), contained in a 500-ml erlenmeyer flask, was warmed to bring the solid into solution, mixed thoroughly by swirling, and placed in a boiling water bath for 2 hr. The mixture was poured with stirring into an ice–water mixture. The precipitated solid was collected by filtration with suction, washed thoroughly with ice-cold water, and air-dried to yield 12 g of tan microcrystalline powder (theory 11.6 g).

The nitration product (10 g) was boiled with ethanol and separated into "alcohol-soluble" and "alcohol-insoluble" fractions. The alcoholic extract yielded a yellow solid, mp 136–146°, which after several recrystallizations from 1:1 methanol–ethanol gave 3 g (30%) of solid, mp 152–153°. The melting point was depressed to 129–131° by mixing with *o*-nitropicrylbenzene but was not depressed when mixed with *m*-nitropicrylbenzene. This was thought to be a crude or polymorphic form of *m*-nitropicrylbenzene, but its nmr spectrum showed that it contained all three isomers in about the same proportions as the crude nitration mixture. Recrystallization from several solvents did not effect further purification. The "alcohol-insoluble" fraction (3 g, mp 175–185°) was recrystallized from 3:1 methanol–ethanol and gave 1.5 g (15%) of pure *p*-nitropicrylbenzene, identified by its nmr spectrum and its mp 199–200°, undepressed when mixed with authentic material.

Tests of Stability of Product Isomers.—About 150 mg of each of the isomeric nitropicrylbenzenes was dissolved in a mixture of glacial acetic acid and concentrated nitric acid taken in the same proportions as for the nitration (10 ml of each per gram of solid). The mixtures, contained in 18 × 150 mm test tubes, were heated in a boiling water bath for 2 hr. Distilled water was added dropwise to the hot solutions to the point of incipient crystallization. The mixtures were allowed to cool thoroughly. The crystalline material in each test tube was collected by filtration with suction, washed thoroughly with cold water, and dried in an oven at 80°. Weights, melting points, and nmr spectra were obtained.

Details are presented in Table III. The nmr spectra of the recovered materials were the same as those of the starting materials. There was no evidence of nitration, and the small losses are attributable to solubility in the media.

TABLE III

TESTS OF STABILITY OF NITROPICRYLBENZENES TO NITRATING CONDITIONS

	Isomer		
	Ortho	Meta	Para
Initial wt, mg	171.5	157.4	146.6
Initial mp, °C	172–173	181–184	200–202
Recovered wt, mg	154.4	141.4	122.2 (141.0)[a]
Recovered, %	90	90	83 (96)[a]
Recovered mp, °C	172–173	181–184	200–202

[a] Including a second crop, mp 199–202°, recovered from the filtrate after dilution with water.

Nmr spectra were obtained with a Varian A-60 nmr spectrophotometer. Solids were dried in a vacuum (oil pump) at 100° (boiling water bath) before preparation of the solutions. The dimethyl sulfoxide (DMSO) used as solvent was scanned at high amplification and was found to be free of absorption in the aromatic region. About 100 mg of each solid was dissolved in about 0.5 ml of DMSO. The solutions were estimated to be about 20% by weight and about 0.5 *M*. Special care was taken to eliminate pen drift during integration by balancing of the detector zero and detector phase circuits. For additional details, see text.

Registry No.—1, 29128-23-2; *o*-nitropicrylbenzene, 24322-55-2; *m*-nitropicrylbenzene, 24322-58-5; *p*-nitropicrylbenzene, 24322-57-4.

Control of the Site of Alkylation of Ambident Anions

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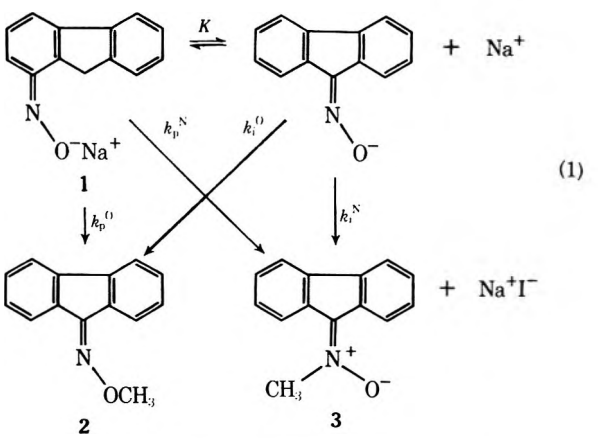
The reaction of sodium 9-fluorenone oximate with methyl iodide in 33.5% acetonitrile and 66.5% *tert*-butyl alcohol solvent at 25.0° gives a concentration dependent second-order rate constant and ratio of oxygen to nitrogen alkylation. The addition of stoichiometric amounts of dibenzo-18-crown-6 polyether eliminates the concentration dependence of the kinetic parameters over the region investigated, presumably by increasing the effective degree of dissociation of the sodium oximate. Sodium tetraphenylboride serves to depress the dissociation of the oximate salt and permits evaluation of the kinetic parameters for associated oximate. Methyl iodide is found to be more reactive toward the free ion than methyl *p*-toluenesulfonate, $k_i(\text{MeOTs})/k_i(\text{MeI}) = 0.68$, while the two reagents have nearly the same reactivity toward the associated sodium oximate, $k_p(\text{MeOts})/k_p(\text{MeI}) = 1.2$.

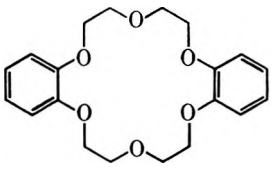
An understanding[1,2] of the interplay of the effect of cation,[3,4] solvent,[3-6] and alkylating agents[3-6] in the reactions of ambident anions is facilitated by studies which allow the dissection[1,4,7] of the overall reaction rate and product ratios into terms due to associated and dissociated ions. Failure to make this separation results in attempts to provide theoretical treatments[8,9] of rate levels and product selectivities of a series of reactions, each member of which may be proceeding through a different blend of reactants.

In a previous paper,[1] the alkylation[10] of sodium 9-fluorenone oximate (1) with methyl iodide in 33.5% acetonitrile–66.5% *tert*-butyl alcohol solvent at 25.0° (eq 1) was reported. This system displays a second-order rate constant which decreases by a factor of 8 as the concentration of sodium 9-fluorenone oximate is increased from 1×10^{-3} *M* to 88×10^{-3} *M*, suggesting that the dissociated ion is more reactive than the associated species. Furthermore, oxygen alkylation to form the *O*-methyl ether 2 was found to decrease from 65 to 46% over this concentration range.

Quantitative dissection of these data into contributions from free and associated ions requires extrapolation to very low and very high sodium oximate concentrations based on the shape of rate and product *vs.* concentration curves. In the present work, the use of



dibenzo-18-crown-6 polyether[11] (4) to promote dissociation[12] and of sodium tetraphenylboride to suppress dissociation[13] is outlined.



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Results and Discussion

The degree of dissociation of salts in a given solvent is influenced by, among other things, specific cation–anion interactions and the effective size of each ion.[14] Therefore, it is anticipated that the addition of dibenzo-18-crown-6 polyether (4) to a solution of sodium 9-fluorenone oximate in 33.5% *tert*-butyl alcohol–66.5% acetonitrile solvent would greatly increase the degree of dissociation[12] of the oximate salt.

Spectra.—A marked change in the color, indicative[12] of a change in the degree of dissociation, of a solution of the dissociation of sodium oximate 1 is observed upon addition of an equivalent amount of crown ether 4. The visible absorption spectrum (Figure 1) indicates that the presence of crown ether results in a shift of a shoulder at 424 nm in sodium oximate 1 to a separate

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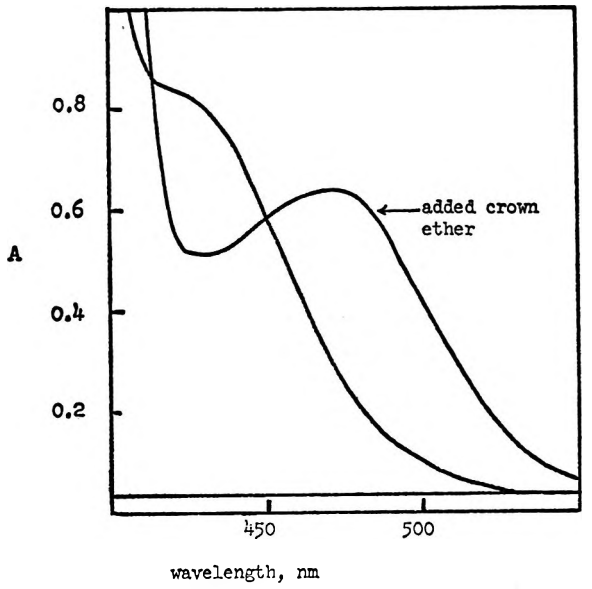

Figure 1.—Plot of absorbance *vs.* wavelength for 5×10^{-3} *M* sodium 9-fluorenone oximate in 66.5% acetonitrile-33.5% *tert*-butyl alcohol solvent with and without added dibenzo-18-crown-6 ether.

band with λ_{max} at 470 nm. Such shifts of absorption to longer wavelengths are characteristic of increased ion separation.[12]

Methyl Iodide.—Reaction kinetics provide further indications that the apparent degree of dissociation of sodium 9-fluorenone oximate in acetonitrile–*tert*-butyl alcohol solvent is markedly increased by the addition of stoichiometric amounts of crown ether III. As summarized in Table I, the observed second-order rate constant for alkylation with methyl iodide at 25.0° in the presence of the crown ether is constant, within experimental error, over a 14-fold variation in initial salt concentration. In the absence of the complexing ether, the observed second-order rate constant would have changed by a factor of *ca.* 2 over this concentration range. In addition, the rate level is substantially increased by added crown ether. For example, with 7×10^{-3} *M* sodium oximate solutions, complexing the sodium ion increases the observed rate constant by a factor of about 15.

The products of the reaction of methyl iodide with sodium 9-fluorenone oximate in the presence of the crown ether also reflect the properties of dissociated ions, with 64% alkylation on oxygen being observed, in agreement with previous estimates based on extrapolation to infinite dilution of 65% O- and 35% N-alkylation.

The addition of a salt such as sodium tetraphenylboride which has a large anion is the counterpart to increasing the effective size of the sodium ion to promote dissociation.[13] Sodium tetraphenylboride serves as a good source of free sodium ion to depress the dissociation of sodium 9-fluorenone oximate and permits exploration of the properties of the aggregated species. The data, summarized in Table I, indicate that with a *ca.* tenfold excess of $Na(C_6H_5)_4B$ the second-order rate constant for reaction with methyl iodide in this solvent system is depressed by a factor of 70 from that observed in the presence of the crown ether. In the presence of excess sodium ion the products now have the composition expected from the alkylation of the ion pair, with N-methylation (68%) dominating.

TABLE I

SUMMARY OF RATE CONSTANTS AND PRODUCTS FOR THE REACTION OF SODIUM FLUORENONE OXIMATE WITH METHYL IODIDE OR METHYL TOSYLATE IN 33.5% ACETONITRILE–*tert*-BUTYL ALCOHOL AT 25°

10^1[oximate], *M*	10^1[CPE],[a] *M*	10^1[NaBPh$_4$], *M*	10^2k_2, l./mol sec	Oxygen-methylation, % yield
		Methyl Iodide		
50	51		97 ± 5[b]	64
46	48		88 ± 9	65
24.3	25.6		105 ± 4	61
14.9	15.5		110 ± 20	66
7.5	8.2		108 ± 5	65
3.6	4.1		99 ± 5	65
9.0		7.7	1.37 ± 0.02	46
9.3		10.1	1.44 ± 0.02	43
9.7		10.6	1.4 ± 0.1	
9.7		14.0		41
9.1		15.0	1.34	41
9.5		17.0		40
		Methyl Tosylate		
55.8	56.1		66 ± 1	97
53.0	52.5		54 ± 3[c]	
25.5	28.0		61 ± 1	98
21.4	22.5		69 ± 0.1	
17.4	19.0		67 ± 4	99
10.0	11.0		67 ± 4	99
9.8	10.5		69	
5.3	5.6		69	99
5.2	5.1		60 ± 1[c]	95
9.0		7.7	1.5 ± 0.1	48
9.3		10.1	1.59 ± 0.04	45
9.7		10.6	1.67 ± 0.01	
9.5		14.2	1.9 ± 0.1	
9.1		15.0		42
9.5		17.0		43

[a] Dibenzo-18-crown-6 polyether. [b] Error given is average deviation. [c] CPE not in excess.

Although supporting direct measurements of the state of aggregation of the crown ether complex of sodium 9-fluorenone oximate in this mixed *tert*-butyl alcohol–acetonitrile solvent are lacking, the spectral shifts, high rate levels, concentration independent second-order rate constants, and high fraction of oxygen alkylation suggest either that the salt is essentially completely dissociated under the conditions employed in these experiments or that, because of the properties of the complexed cation, associated species have kinetic reactivities closely approximating those of dissociated ions.

Methyl *p*-Toluenesulfonate.—The nature of the leaving group is known to affect the relative rate of alkylation at the two sites of an ambident anion.[3-6] The tendency of enolate ions to give largely oxygen alkylation with alkyl toluenesulfonates, carbon alkylation with alkyl toluenesulfonates, and carbon alkylation with alkyl iodides has been rationalized by a symbiotic effect[8] in which the hard oxygen center of the enolate ion reacts preferentially with alkylating agents with a leaving group such as toluenesulfonate which is classed as hard; and, in this terminology, the relatively soft carbon atom has enhanced reactivity toward those alkylating agents, such as methyl iodide, which have a soft leaving group.

Pearson and Songstad[8] have suggested that the ratio of rate constants for reaction with alkyl tosylates compared to alkyl iodides, k_{OTs}/k_I, is a rough guide to the hard–soft character of a reactant. Since the observed rate constant and composition of the product mixture resulting from the alkylation of oximates is a function of the state of association of the oximate salt, it is of interest to compare the reaction of methyl iodide with methyl *p*-toluenesulfonate.

As summarized in Table I, the reaction of methyl *p*-toluenesulfonate, like methyl iodide, gives a second-order rate constant which is essentially independent of oximate concentrations from 5×10^{-3} to 5×10^{-2} *M* when 1 equiv of dibenzo-18-crown-6 polyether is present. Only O-methylation was detected over the concentration region investigated when the sodium ion was complexed with crown ether. Excess sodium tetraphenylboride depresses k_{obsd} by a factor of *ca.* 40 and changes the product from 99% oxygen to 54% nitrogen methylation.

To the extent that the observed rate constant in the presence of crown ether may be identified as k_i, the rate constant for reaction of dissociated oximate ion, and to the extent that those rate constants measured in the presence of excess sodium tetraphenylboride correspond to k_p, the rate constant for reaction of sodium 9-fluorenone oximate ion pair, it is possible to compare the reactivities of methyl *p*-toluenesulfonate and methyl iodide toward the free and associated ion. Toward the free ion, methyl tosylate is not so reactive as methyl iodide, $k_i(\text{MeOTs})/k_i(\text{MeI}) = 0.68$, while the two reagents have nearly the same reactivity toward the associated sodium oximate, $k_p(\text{MeOTs})/k_p(\text{MeI}) = 1.2$. That is, the gap between k_i and k_p, as measured by these techniques, is smaller for methyl tosylate than for methyl iodide. Although many additional factors may be involved, this result may be rationalized by postulating an enhanced reactivity for the sodium oximate ion pair with methyl tosylate because of the formation of a relatively tight sodium *p*-toluenesulfonate ion pair.

Dissecting the values of k_i and k_p further into rate constants for reaction on oxygen and nitrogen by multiplying the observed rate constants by the corresponding fraction of reaction at each site indicates that for the free ion the major difference between the two alkylating agents lies in the reactivity at nitrogen. Both reagents react at oxygen at the same rate, within experimental error; *e.g.*, $k_i^O(\text{MeOTs})/k_i^O(\text{MeI}) = 1.0$. Methyl iodide, however, gives an additional 35% N-alkylation, while no reaction at nitrogen through the free ion is observed with methyl tosylate, $k_i^N(\text{MeOTs})/k_i^N(\text{MeI}) = 0$.

In marked contrast to the properties of the free ion, the associated sodium 9-fluorenone oximate reacts with methyl tosylate and methyl iodide at nearly the same rate and gives essentially the same ratio of oxygen to nitrogen alkylation. This behavior is reflected in the value of $k^N(\text{MeOTs})/k^N(\text{MeI})$ which is zero for the free ion and 1.2 for the associated species. Therefore, the classification of the hard–soft character of the two sites in this oximate, by the criterion of Pearson and Songstad,[8] depends on the state of aggregation of the ambident ion, possibly because of an interaction between the leaving group and the cation of the ion pair.

Experimental Section

Materials.—Dibenzo-18-crown 6 ether was prepared by method X of Pederson[11] in 24% yield, mp 162–163° (lit.[11] mp 164°) after recrystallization from tetrahydrofuran. 9-Fluoreneone oxime was prepared as previously described.[1] The solvent mixture used (33.5% CH_3CN–66.5% *tert*-butyl alcohol) has also been described.[1]

Solution Preparation.—Solutions of appropriate approximate concentrations were made by adding measured volumes of sodium *tert*-butoxide solution, acetonitrile, and mixed solvent to weighed amounts of oxime and crown ether or sodium tetraphenylboride in bottles equipped with silicon rubber serum caps. The precise oximate concentration was then determined by titrating an aliquot with standard HCl, with metacresol purple being used as an indicator. Prepared solutions were used immediately.

Kinetics.—Samples of the prepared solutions were placed in silicon rubber serum capped spectrometer cells or, in the case of slow-reacting solutions, into small bottles similarly capped. These samples were equilibrated in a thermostated bath at 25.0°. An appropriate amount of methyl iodide or methyl tosylate was added to an equilibrated sample with a microliter syringe and a cell filled with the mixture was placed in a spectrometer. The absorbance change was followed at an arbitrarily selected wavelength between 435 and 470 nm. A scale expander was used to increase the apparent change for dilute solutions. The temperature of the cell block was controlled to 25.00 ± 0.02° with a proportional temperature control.

The oximate remaining after at least ten reaction half-lives was titrated with standard HCl and the quantity of alkylating agent was determined by difference. For the dilute solutions, a 5-ml sample was titrated; 1 ml was titrated for the more concentrated solutions. An excess of methyl iodide was added to the reacting solution after the infinity value had been determined and a baseline correction had been found and applied to all absorbance readings.

Spectra.—The spectra of the ion pair and the free ion were recorded with a 1-cm cell in a Perkin-Elmer Model 202 spectrometer.

Product Determination.—Products were determined by the method described by Smith and Milligan.[1]

Registry No.—**4,** 14187-32-7; sodium 9-fluorenone oximate, 20474-42-4; methyl iodide, 74-88-4; methyl tosylate, 80-48-8.

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Photochemical Valence Isomerization of a Conjugated Imino Ether

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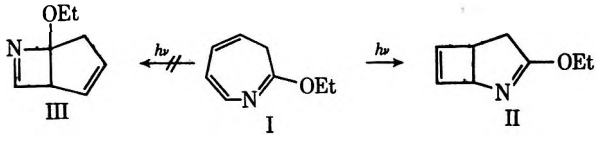
A photochemical valence isomerization of a heterodiene, 4,5-dihydro-2-ethoxy-4,4,6-trimethyl-3*H*-azepine (IV), to a 1-azetine derivative VI is described. The heterodiene is photostable in the excited singlet state and the valence isomerization reaction only occurs under conditions of photosensitization.

Photochemical valence isomerization of cisoid 1,3-dienes is a generally useful method for the preparation of cyclobutene derivatives. Examples have been reported for acyclic, cyclic, and heterocyclic dienes.[1,2] Few cases, however, are known in which a heteroatom is part of the diene chromophore.[3-5] Odum and Schmall recently reported that irradiation of 2-ethoxy-3*H*-azepine (I) yields 3-ethoxy-2-azabicyclo[3.2.0]-hepta-2,6-diene (II) as the exclusive valence isomerization product. The product of participation of the imino ether, 5-ethoxy-6-azabicyclo[3.2.0]hepta-2,6-diene (III), was not observed.[6] In this paper we

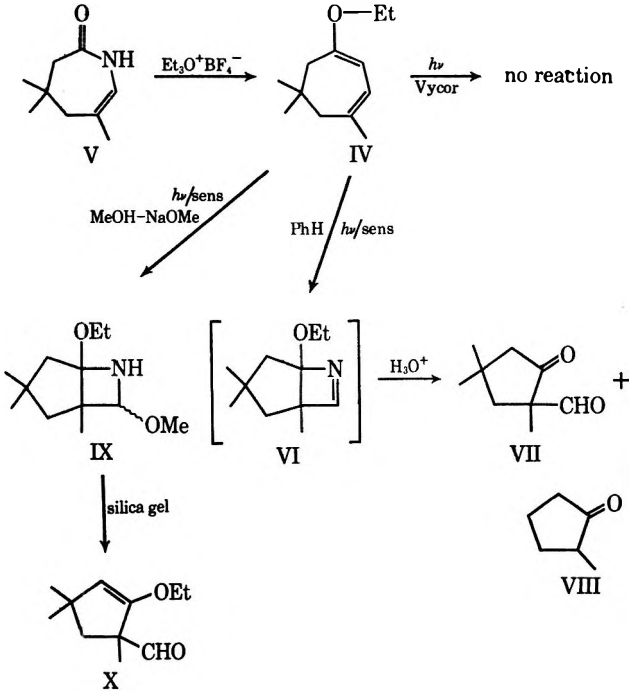


report evidence for the participation of an imino ether group in a valence isomerization reaction.

In our investigations of the photochemical reactivity of conjugated imines and imino ethers,[7] we have looked at the photochemical reactivity of 4,5-dihydro-4,4,6-trimethyl-3*H*-azepine (IV). The dihydroazepine was prepared in 86% yield by the O-alkylation of 4,5-dihydro-4,4,6-trimethyl-2(3*H*)-azepin-2-one (V) with Meerwein's salt. The structure of IV is established by the spectroscopic data. The unsaturated imino ether shows strong infrared absorption at 6.15 μ and ultraviolet absorption at 252 nm (ϵ 3900). In the nmr IV exhibits a six-proton singlet at δ 1.00 for the gem dimethyl group, a three-proton triplet (J = 7 Hz) at δ 1.25 and a two-proton quartet (J = 7 Hz) at δ 4.11 for the ethoxy group, an allylic methylene absorption at δ 1.71 (singlet), a three-proton doublet (J = 1.5 Hz) at δ 1.79 for the allylic methyl, a two-proton singlet at δ 2.03 for the methylene adjacent to the imino ether group, and an olefinic absorption (broad) at δ 6.02. Coupling between the allylic and olefinic protons was demonstrated by double resonance.

Irradiation of dihydroazepine IV in anhydrous ether with a 450-W mercury lamp equipped with a Vycor filter resulted in virtually no destruction of starting material. However, when a photosensitizer (either benzophenone or acetophenone) was employed, efficient photodestruction of IV occurred. Evaporation of the irradiation solvent (benzene) yielded an oil which polymerized upon standing or upon attempted distillation. Immediate treatment of the oil with 3 *N* hydrochloric acid at 50° yielded two stable, volatile products which were extracted and isolated by preparative gas chromatography. The products were identified as 2-formyl-2,4,4-trimethylcyclopentanone (VII) and 3,4,4-trimethylcyclopentanone (VIII) by comparison of ir and nmr spectra with those of authentic samples prepared by acid-catalyzed isomerization of isophorone oxide.[8] Formation of the β-ketoaldehyde VII upon hydrolysis of the irradiation mixture suggests that the photoproduct of the dihydroazepine IV is in fact the valence isomer, 1-ethoxy-3,3,5-trimethyl-7-azabicyclo-[3.2.0]hept-6-ene (VI). The trimethylcyclopentanone hydrolysis product VIII occurs by a reverse aldol condensation of the β-ketoaldehyde (Scheme I).

SCHEME I



Photochemical valence isomerization of IV was further substantiated by irradiation in anhydrous methanol solution in the presence of 1% sodium methoxide and a photosensitizer, benzophenone. Under these conditions a solvent addition product of the valence isomer, 1-ethoxy-6-methoxy-3,3,5-trimethyl-7-azabicyclo[3.2.0]heptane (IX), was isolated. The sol-

(1) R. Srinivasan, *Advan. Photochem.*, **4**, 113 (1966).

(2) G. J. Fonken in "Organic Photochemistry," Vol. 1, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967, p 197.

(3) 1-Azetine derivatives have been reported by C. Lohse, *Tetrahedron Lett.*, 5625 (1968); bicyclic 2-azetines have been obtained by J. Derocque, W. J. Theiser, and J. A. Moore, *J. Org. Chem.*, **33**, 4381 (1968).

(4) 1-Oxetenes have been reported by O. L. Chapman and W. R. Adams, *J. Amer. Chem. Soc.*, **90**, 233 (1968); J. M. Holouka, P. D. Gardner, C. B. Strow, M. L. Hill, and T. V. Van Auken, *ibid.*, **90**, 5041 (1968); and L. E. Friedrich and G. B. Schuster, *ibid.*, **91**, 7204 (1969).

(5) A four-membered-ring azoxy compound has been reported by W. R. Dolbier, Jr., and W. M. Williams, *ibid.*, **91**, 2818 (1969).

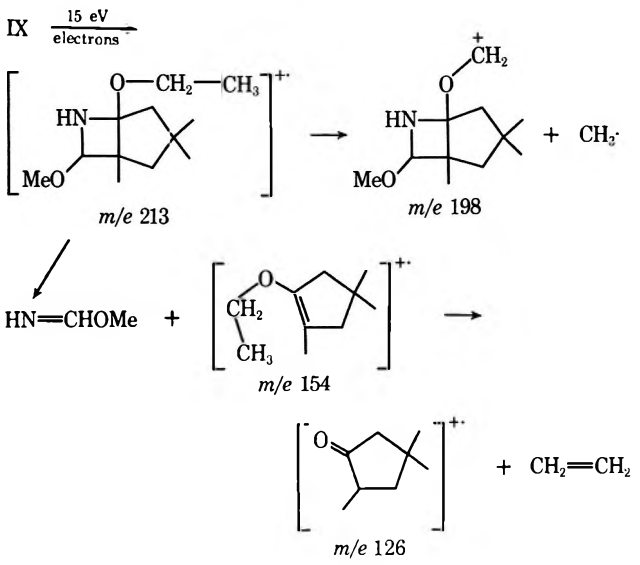
(6) R. A. Odum and B. Schmall, *Chem. Commun.*, 1299 (1969).

(7) For the previous paper in this series, see T. H. Koch and R. J. Sluski, *Tetrahedron Lett.*, 2391 (1970).

(8) H. O. House and R. L. Wasson, *J. Amer. Chem. Soc.*, **79**, 1488 (1957).

vent addition product exhibits an N–H stretching vibration at μ 3.02 and no olefinic or imino ether stretching vibrations in the infrared spectrum. In the nmr three methyl singlets appear at δ 1.02, 1.07, and 1.15. The two sets of methylene protons occur as two AB patterns with chemical shifts of δ 1.52 and 1.72 (J = 14 Hz) and 1.63 and 1.83 (J = 14 Hz). The ethoxy group appears as a triplet at δ 1.12 and a quartet at δ 3.57 (J = 7 Hz), and the methoxy protons appear as a three-proton singlet at δ 3.16. The methine proton is shifted by the two adjacent heteroatoms to δ 4.20, and the N–H proton appears as a broad absorption at δ 2.88. The mass spectrum (direct probe, 15 eV) exhibits only a weak parent ion at m/e 213 (2% of base). The three most intense fragments occur at m/e 198 (20% of base), 154 (37% of base), and 126 (base), and the fragment at m/e 154 is related to the peak of m/e 126 by a metastable ion at m/e 103 (calcd 103). The fragmentation sequence can be explained as indicated in Scheme II.

SCHEME II



The methanol addition product is not stable to silica gel chromatography. When IX was eluted from a column of tlc grade silica gel at 100 psi with 30% chloroform–70% benzene solvent, a product of partial hydrolysis, 2-ethoxy-3-formyl-3,5,5-trimethylcyclopentene, was isolated. This product was also identified spectroscopically. In the infrared, aldehydic and olefinic stretching vibrations occur at 5.78 and 6.09 μ, respectively. Methyl singlets are observed at δ 1.08, 1.13, and 1.23, the methylene protons at δ 1.42 and 2.15 (AB pattern, J = 14 Hz), and the ethoxy group at δ 1.30 (triplet, J = 7 Hz) and 3.76 (quartet, J = 7 Hz). The olefinic proton appears as a one-proton singlet at δ 4.44, characteristic of olefinic protons of vinyl ethers. We note that a geminal coupling constant of 14 Hz is consistently observed in the five-membered ring compounds VIII, IX, and X.

We feel that the structural evidence firmly supports the fact that IV is undergoing an electrocyclic reaction to form an unstable 1-azetine derivative. Electrocyclic reactions of cisoid dienes in excited states are symmetry allowed for the disrotatory mode of closure. Alternatively, photochemical cis–trans isomerization followed by thermal conrotatory ring closure is also a symmetry-allowed process, both mechanisms yielding the same product.[9] Since our reaction occurs exclusively from the triplet state, it is especially important to consider the latter mechanism. Sensitized and unsensitized cis–trans isomerizations have been reported in seven- and eight-membered carbocyclic systems.[10–18] Conrotatory ring closure was sometimes a subsequent reaction.[17,18] In an effort to distinguish between the two modes of ring closure, we attempted to trap a possible geometric isomer with furan, a method proved successful by other research groups.[12,18] A mixture of acetophenone and dihydroazepine was sprayed on an aluminum plate at −190° within a vacuum shroud and irradiated through a Pyrex filter with an external, 200-W super pressure mercury lamp for 30 min. While still at liquid nitrogen temperature, furan was then sprayed on the plate and the mixture slowly allowed to warm to room temperature. No furan addition products were isolated from the irradiated mixture. Although the experiment does not eliminate the possibility of geometrical isomerization prior to ring closure, it does suggest that, if cis–trans isomers are formed, they are not stable at liquid nitrogen temperature. A high degree of instability is predicted for a cis–trans isomer since the isomerization would force a methyl group toward the center of the ring.

Additional studies on photochemical reactivity of other conjugated imine and imino ether systems are currently under way.

Experimental Section

Melting points and boiling points are uncorrected. Melting points were measured with a Thomas-Hoover Unimelt apparatus. Perkin-Elmer Model 337 and Cary 14 spectrophotometers were used to determine ir and uv spectra, respectively. Nmr spectra were recorded with Varian A-60A and HA-100 spectrometers and chemical shifts are reported in δ units from internal tetramethylsilane. The mass spectra were obtained with Varian Mat CH-4 and CH-7 spectrometers. Glpc analyses and isolations were performed with a Varian Aerograph (Model 200) gas chromatograph equipped with a thermal conductivity detector, and peak areas were measured by Disc integration. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Materials.—4,5-Dihydro-4,4,6-trimethyl-2(3*H*)-azepine was prepared by the Beckman rearrangement of the anti oxime of isophorone according to the procedure of Mazur.[19] Reagent grade benzene was purified for irradiation purposes by stirring with concentrated sulfuric acid for several days, extracting with water and saturated sodium bicarbonate solution, drying over sodium hydroxide, and distilling from phosphorus pentoxide.

4,5-Dihydro-2-ethoxy-4,4,6-trimethyl-3*H*-azepine (IV).—A procedure analogous to that reported by Paquette for the prep-

(9) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).
(10) E. J. Corey, M. Tada, R. LeMahieu, and L. Libit, *J. Amer. Chem. Soc.*, **87**, 2051 (1965).
(11) P. Eaton and K. Lin, *ibid.*, **86**, 2087 (1964).
(12) P. Eaton and K. Lin, *ibid.*, **87**, 2052 (1965).
(13) P. Datta, T. D. Goldfarb, and R. J. Beikess, *ibid.*, **91**, 5429 (1969).
(14) E. H. White, E. W. Friend, Jr., R. L. Stern, and H. Maskill, *ibid.*, **91**, 523 (1969).
(15) G. M. Whitesides, G. L. Goe, and A. C. Cope, *ibid.*, **91**, 2608 (1969).
(16) W. J. Nebe and G. J. Fonken, *ibid.*, **91**, 1249 (1969).
(17) R. S. H. Liu, *ibid.*, **89**, 112 (1967).
(18) L. L. Barber, O. L. Chapman, and J. D. Lassila, *ibid.*, **91**, 537 (1969).
(19) R. H. Mazur, *J. Org. Chem.*, **26**, 1289 (1961).

aration of 2-ethoxy-3,5,5-trimethyl-3*H*-azepine was followed.[20] All glassware was oven-dried prior to use. A 500-ml three-neck flask was charged with 41 g (0.28 mol) of freshly distilled boron trifluoride etherate and 135 ml of anhydrous ether (distilled from lithium aluminum hydride). The reaction vessel was equipped with addition funnel, condenser, stirring apparatus, and drying tube. Epichlorohydrin (20 g, 0.22 mol) was added dropwise with stirring. Upon completion of the addition, the reaction mixture was stirred at room temperature for an additional 3 hr. At this time the triethyloxonium fluoroborate was crystalline. The ether was pipetted off and the crystals were washed three times with anhydrous ether. The triethyloxonium fluoroborate was partially dissolved in 20 ml of dry methylene chloride (freshly distilled from calcium hydride), and a solution of 27.8 g (0.20 mol) of 4,5-dihydro-4,4,6-trimethyl-2(3*H*)-azepin-2-one [mp 90–91° (lit.[19] 89–91°)] in 90 ml of dry methylene chloride was added dropwise while the reaction mixture was maintained at 10–15 with a water bath. The resulting solution was stirred at room temperature for 1 hr and allowed to stand overnight. The reaction was then hydrolyzed by dropwise addition of 35 g of 50% potassium hydroxide solution. The precipitate was removed by filtration and the filtrate dried with anhydrous sodium sulfate. After rotary evaporation of the methylene chloride, the residual oil was fractionally distilled at 9 mm as follows: fraction 1, 3.4 g, bp 66–69°; fraction 2, 7.9 g, bp 69–83°; and fraction 3, 21.0 g, bp 83°. The fractions were analyzed with a 7 ft × 0.25 in. column of 10% Carbowax 20M on 60–80 mesh Chromosorb W at 140°, helium flow 60 cc/min. Fractions 1 and 2 were found to consist of three products and to have the following compositions in order of retention time 20, 44, 31, and 8, 76, 18%, respectively. The compositions are uncorrected for differences in thermal conductivity. The second peak in the chromatogram was identified as the desired oxygen alkylation product, 4,5-dihydro-2-ethoxy-4,4,6-trimethyl-3*H*-azepine. Distillation fraction 3 consisted entirely of this product. The first and third peaks were collected from the gas chromatograph (10 ft × 3/8 in. column of 10% Carbowax 20M on 60–80 mesh Chromosorb W at 155°, helium 60 cc/min) and identified as 1-chloro-2,3-diethoxypropane and 3-chloro-2-ethoxypropanol, respectively. The total yield of the dihydroazepine product IV including fractions 1 and 2 was 86%. An analytical sample of IV was collected from the gas chromatograph as described above for the by-products: nmr (CCl_4) δ 1.00 (singlet, 6 H), 1.25 (triplet, J = 7 Hz, 3 H), 1.71 (singlet, 2 H), 1.79 (doublet, J = 1.5 Hz, 3 H), 2.03 (singlet, 2 H), 4.11 (quartet, J = 7 Hz, 2 H), 6.02 (multiplet, 1 H); ir (neat) 3.40, 6.15, 7.32, 7.67, 8.10, 8.50, 9.0, and 9.6 μ; uv λ_{max}^{EtOH} 252 nm (ϵ 3900).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 73.09; H, 10.52; N, 7.80; mol wt, 181 (mass spectrum).

Irradiation in the Absence of a Sensitizer.—A solution of 1.0 g of 4,5-dihydro-2-ethoxy-4,4,6-trimethyl-3*H*-azepine in 120 ml of anhydrous ether was irradiated for 4 hr with a Hanovia 450-W lamp equipped with a Vycor filter. Destruction of the starting dihydroazepine IV was monitored by glpc with a column of 10% Carbowax 20M on 60–80 mesh Chromosorb W at 140° (He 60 cc/min). The gas chromatographic analysis indicated no photodestruction of starting material. Upon evaporation of the solvent, 4,5-dihydro-2-ethoxy-4,4,6-trimethyl-3*H*-azepine (0.95 g) was recovered, pure by glpc and nmr.

Irradiation in the Presence of Acetophenone.—A solution of 2.0 g of 4,5-dihydro-2-ethoxy-4,4,6-trimethyl-3*H*-azepine and 0.23 g of acetophenone in 100 ml of purified benzene was irradiated for 2.25 hr with a 450-W Hanovia lamp equipped with a Corex filter. The destruction of starting material was followed by glpc. After rotary evaporation of the solvent, 10 ml of 3 *N* hydrochloric acid was added and the mixture was heated with stirring at 50° for 0.5 hr. The reaction mixture was cooled, neutralized with saturated sodium bicarbonate solution, and extracted three times with ether. The combined ether extracts were dried with magnesium sulfate, and the ether was removed by rotary evaporation. The resulting oil was distilled at 15-mm pressure by Kugelrohr distillation and three fractions were collected: fraction 1, room temperature (0.10 g); fraction 2, room temperature to 91° (0.36 g); and fraction 3, 92–125° (0.33 g). Each fraction was analyzed on glpc with a 10% Carbowax 20M on 60–80 mesh Chromosorb W column at 150° (He, 67 cc/min) and found to contain the following per cent composition of 2,4,4-trimethylcyclopentanone, 2-formyl-2,4,4-trimethylcyclopentanone, and acetophenone, respectively: fraction 1, 89, 7, 4%; fraction 2, 39, 43, 18%; fraction 3, 14, 60, 26%. The percent compositions are uncorrected for differences in thermal conductivity. The uncorrected yields for 2,4,4-trimethylcyclopentanone and 2-formyl-2,4,4-trimethylcyclopentanone were both 21%, giving a total yield of 42% hydrolysis products. The yield of recovered acetophenone was 67%. 2,4,4-Trimethylcyclopentanone shows nmr (CCl_4) absorptions at δ 1.05 (doublet, J = 7 Hz, 3 H), 1.10 (singlet, 3 H), 1.18 (singlet, 3 H), 1.98 (singlet, 2 H), 1.2–2.7 (complex pattern, 3 H). 2-Formyl-2,4,4-trimethylcyclopentanone shows nmr (CCl_4) absorptions at δ 1.05 (singlet, 3 H), 1.17 (singlet, 3 H), 1.34 (singlet, 3 H), 1.50 and 2.62 (AB pattern, J = 14 Hz, 2 H), 2.12 (singlet, 2 H), 8.71 (singlet, 1 H). Both hydrolysis products were unambiguously identified by comparison of their nmr and ir spectra with samples prepared by boron trifluoride etherate catalyzed rearrangement of isophorone oxide.[8]

Irradiation in the Presence of Methanol and Sodium Methoxide.—A dry Pyrex tube 18 cm × 7 mm o.d. was charged with 0.212 g of benzophenone (sublimed), 0.249 g of 4,5-dihydro-2-ethoxy-4,4,6-trimethyl-3*H*-azepine, and 3.3 ml of 1.1% sodium methoxide anhydrous methanol solution (methanol distilled from magnesium methoxide prior to use). The tube was attached to a vacuum line with an Ultratorr union and degassed by three freeze (liquid nitrogen), pump (10^{-5} mm), thaw cycles. Upon completion of the degassing, the vacuum line and irradiation tube were filled to 1 atm of prepurified nitrogen. The solution was irradiated for 11 hr at 3500 Å with three external low-pressure mercury lamps (Southern New England Ultraviolet Co.). The irradiated solution was distilled by trap-to-trap distillation on the vacuum line at 7 × 10^{-6} mm. For the distillation, traps of ice, Dry Ice, and liquid nitrogen were employed. The irradiation tube was maintained at 21° with a cold water bath throughout the distillation. In the ice trap was collected 0.051 g of material which consisted of roughly 23% benzophenone and 77% 1-ethoxy-6-methoxy-3,3,5-trimethyl-7-azabicyclo[3.2.0]heptane by nmr analysis. The Dry Ice trap contained methanol and additional azabicyclic product. Redistillation of this fraction on the vacuum line yielded an additional 0.080 g of product. The total yield of product was 0.13 g (45%). An analytical sample of the azabicyclic product was obtained by redistillation of the fraction contaminated with benzophenone: nmr (CCl_4) δ 1.02 (singlet, 3 H), 1.07 (singlet, 3 H), 1.12 (triplet, J = 7 Hz, 3 H), 1.15 (singlet, 3 H), 1.52 and 1.72 (AB pattern, J = 14 Hz), 1.63 and 1.83 (AB pattern, J = 14 Hz), 2.88 (broad absorption, 1 H), 3.16 (singlet, 3 H), 3.57 (quartet, J = 7 Hz, 2 H), 4.20 (singlet, 1 H); ir (neat) 3.02, 3.45, and 8.61 μ; mass spectrum (15 eV) m/e 213 (2% of base), 198 (20% of base), 154 (37% of base), and 126 (base).

Anal. Calcd for $C_{12}H_{23}O_2N$: C, 67.56; H, 10.87; N, 6.57. Found: C, 67.69; H, 10.79; N, 6.70.

When the solvent addition product was chromatographed on a high-pressure (100 psi) silica gel column 0.5-in. i.d. by 23 in. (Chromatronix) eluting with 30% chloroform–70% benzene solvent, a product of partial hydrolysis, 2-ethoxy-3-formyl-3,5,5-trimethylcyclopentene, was isolated: nmr (CCl_4) δ 1.08 (singlet, 3 H), 1.13 (singlet, 3 H), 1.23 (singlet, 3 H), 1.30 (triplet, J = 7 Hz, 3 H), 1.42 and 2.15 (AB pattern, J = 14 Hz), 3.76 (quartet, J = 7 Hz, 2 H), 4.44 (singlet, 1 H), 9.47 (singlet, 1 H); ir (CCl_4) 3.28, 3.40, 3.51, 3.58, 3.71, 5.78, 6.09, 6.92, 7.50, 7.85, 8.37 μ.

Irradiation at Low Temperature.—An aluminum disk attached to a stainless steel dewar within a vacuum shroud (Air Products) was cooled to liquid nitrogen temperature and alternately sprayed with acetophenone and 4,5-dihydro-4.4,6-trimethyl-3*H*-azepine. The mixture was irradiated at liquid nitrogen temperature with an external 200-W super pressure mercury lamp (Bausch and Lomb) through a Pyrex filter for 30 min. While still at liquid nitrogen temperature, the aluminum disk was sprayed with furan and the entire mixture was gradually allowed to warm to room temperature. Tlc analysis of the reaction mixture suggested that furan addition products were not formed. Only dihydroazepine, acetophenone, and polymeric products were observed. Photoreaction of 4,5-dihydro-4,4,6-trimethyl-3*H*-azepine in the presence of acetophenone at liquid nitrogen temperature has been observed by infrared analysis.

Registry No.—IV, 29431-21-8; IX, 29431-22-9; X, 29431-23-0.

(20) L. A. Paquette, *J. Amer. Chem. Soc.*, **86**, 4096 (1964).

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3-Monosubstituted 1-Benzoyl-2,2-dichloroaziridines. Methanolysis, Thermolysis, and Benzoylation

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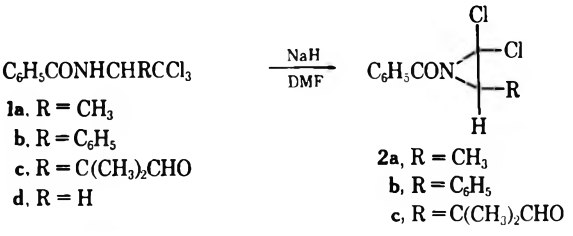
Received November 17, 1970

Three 3-monosubstituted 1-benzoyl-2,2-dichloroaziridines **2** have been prepared by cyclization of the corresponding trichloroethylamides **1**. Their behavior on methanolysis and thermolysis was examined. Unlike the corresponding 1-arylaziridines, acid catalysis is required for the methanolysis of the 1-benzoylaziridines. The course of this reaction is sensitive to the nature of the 3 substituent. Like many other 1-acyl-3-arylaziridines, **2b** rearranges thermally giving the oxazole derivative **8**. In contrast, the 3-alkylaziridines **2a** and **2c** are thermally stable in the absence of acid. A novel ring-opening reaction of **2a** occurs with benzoyl chloride. It is concluded that ring cleavage of the 1-benzoyl-3-alkylaziridines is generally initiated by electrophilic attack at the amide oxygen atom. Curiously, however, acid catalysis leads to C-2–N bond cleavage of the aziridine ring of **2a**, whereas benzoylation results in C-3–N bond rupture.

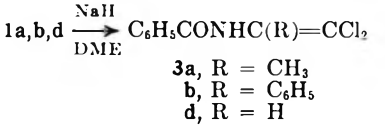
Previous work[1] has demonstrated the ready accessibility of *N*-trichloroethylbenzamides of type **1**. If



the proximity of the amido group could be utilized to facilitate displacement of halogen from the normally inert trichloromethyl group, these compounds might serve as intermediates for a new general synthesis of α-amino acids. While exploring this possibility it was found that treatment with sodium hydride in dimethylformamide (DMF) did indeed lead to the 1-benzoyl-2,2-dichloroaziridines **2** in three examples tried.[2]

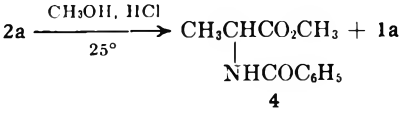
Unfortunately, cyclization was not the exclusive reaction. Some decomposition occurred and elimination of HCl from **1** was not completely preventable. Indeed, in 1,2-dimethoxyethane (DME) as solvent in place of DMF, the amides **1a**, **1b**, and **1d** gave the products of elimination **3a** (27%), **3b** (83%), and **3d** (79%), respectively.[4]

Although achievement of the original objective of this work was clearly thwarted by the poor yields



(45–60%) of **2** obtainable even under the best conditions, further study of the chemistry of these aziridines was of interest. 1-Aryl-2,2-dichloroaziridines have been thoroughly studied,[5,6] and at least one report of 1-benzoyl-monochloroaziridines has appeared.[7] However, the 1-benzoyl-2,2-dichloroaziridines **2** represent a new type worthy of study in view of the reports[8] that 1-aryl-monochloroaziridines differ chemically from their 2,2-dichloro analogs.

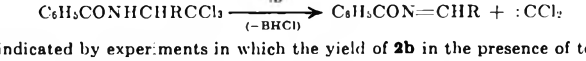
Two reactions were chosen: acid-catalyzed methanolysis and thermolysis. Treatment of the methylaziridine **2a** with methanolic hydrogen chloride at room temperature for 1 week gave two products: *N*-benzoyl-*dl*-alanine methyl ester (**4**) (39% yield, partly hydrolyzed to the acid during isolation) and the trichloroethylamide **1a** (13% yield). Similar treatment of the



phenylaziridine **2b** resulted in more radical rupture of the molecule. Essentially all of the nitrogen was converted to ammonium chloride (93% yield), the 1-benzoyl group appeared as methyl benzoate (90% yield), and the rest of the molecule emerged as a mixture of the chloro ester **5** (53% yield) and the methoxy ester **6**

(1) H. E. Zaugg, *Syn.*, **2**, 49 (1970).

(2) That these cyclizations result from intramolecular nucleophilic displacement of halide ion and not by addition of dichlorocarbene to an acylimine, *i.e.*,



is indicated by experiments in which the yield of **2b** in the presence of tetramethylethylene, although reduced somewhat, is no poorer than the yield obtained in the presence of an equal volume of cyclohexane.[3]

(3) Compare J. A. Deyrup and R. B. Greenwald, *Tetrahedron Lett.*, 321 (1965).

(4) An attractive rationalization for this marked solvent effect involves the reasonable assumption that the sodium derivatives of the amides **1** are largely contact ion pairs in DME and either solvent-separated ion pairs or free ions in DMF. The proximity of the sodium ion in the contact ion pairs could lower the nucleophilic reactivity of the amide anion as well as assist in the removal of chloride ion through a cyclic transition state, with both effects favoring elimination.

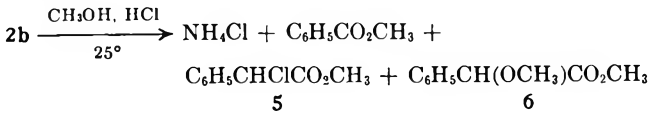
(5) (a) E. K. Fields and J. M. Sandri, *Chem. Ind. (London)*, 1216 (1959); A. G. Cook and E. K. Fields, *J. Org. Chem.*, **27**, 3686 (1962); (b) P. K. Kadaba and J. O. Edwards, *ibid.*, **25**, 1431 (1960); (c) H. W. Heine and A. B. Smith, III, *Angew. Chem., Int. Ed. Engl.*, **2**, 400 (1963); (d) K. Ichimura and M. Ohta, *Tetrahedron Lett.*, 807 (1966); *Bull. Chem. Soc. Jap.*, **40**, 1933 (1967).

(6) R. E. Brooks, J. O. Edwards, G. Levey, and F. Smyth, *Tetrahedron*, **22**, 1279 (1966).

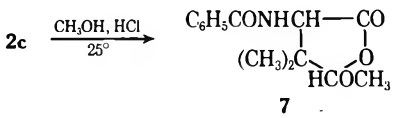
(7) F. W. Fowler and A. Hassner, *J. Amer. Chem. Soc.*, **90**, 2875 (1968).

(8) J. A. Deyrup and R. B. Greenwald, *Tetrahedron Lett.*, 5091 (1966); *J. Amer. Chem. Soc.*, **87**, 4538 (1965).

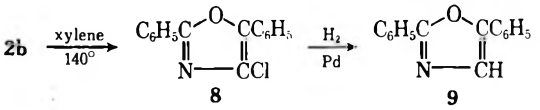
(32% yield). In the absence of acid, **2b** was stable in methanol.



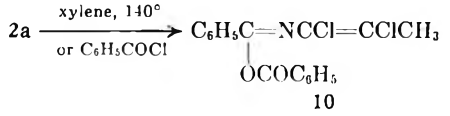
Methanolysis of the aziridine **2c** resembled that of the methyl derivative **2a**. However, the aldehyde and carboxyl groups interacted in the process to give the lactonic acetal **7** as the ultimate product (43% yield).



The thermolytic reactions also varied. In boiling xylene the phenylaziridine **2b** smoothly rearranged to 4-chloro-2,5-diphenyloxazole (**8**, 81% yield), identified by catalytic hydrogenolysis to the known[9] 2,5-diphenyloxazole (**9**). In contrast to **2b**, the aziridine **2c** could be

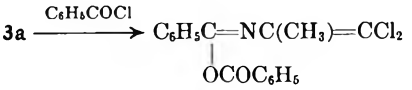


recovered quantitatively from boiling xylene (24 hr). It could be distilled with only slight decomposition using bath temperatures up to 215°. Likewise, the methylaziridine **2a** was distillable under reduced pressure *in the absence of acidic impurities*. On standing for long periods (6 months) even at room temperature, both **2a** and **2c** slowly decomposed with the evolution of acidic fumes. A solid product of this acid decomposition of **2a** proved to be the trichloroamide **1a**. In boiling xylene **2a** slowly evolved hydrogen chloride, and from the largely decomposed reaction mixture four crystalline compounds could be isolated: benzoic acid, benzamide, the trichloroamide **1a**, and a very poor yield of a compound, mp 160–161°, to which the structure **10** (cis or trans) has been assigned on the basis of



spectral and microanalytical data (see Experimental Section). Further support for this assignment was derived (1) from the observed formation of methyl benzoate by the base-catalyzed methanolysis of **10**, (2) from acid hydrolysis of **10** to an amide possessing the spectral properties and elemental composition required of structure **11**, yet different from the isomeric **3a**, and

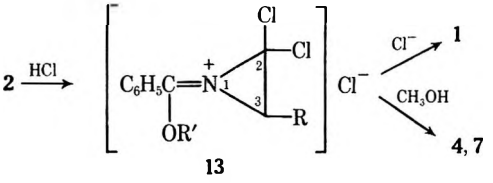
(3) from the observation that a better yield (32%) of **10** was obtainable by treatment of the aziridine **2a** directly with benzoyl chloride. Also obtained in this reaction was an 11% yield of a homogeneous oil whose ir, nmr, and mass spectra were similar to those of **10**. That this oil is the other isomer of structure **10** was shown by its nonidentity with the only possible alternative, *i.e.*, **12**, prepared by benzoylation of the amide **3a**.



Discussion

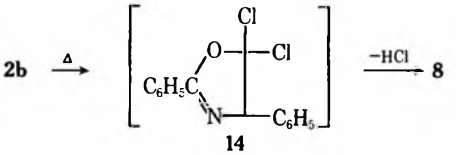
A thorough mechanistic study[6] of the solvolysis of 2,2-dichloro-1,3-diarylaziridines provided strong evidence for the intermediacy of a nonexchanging ion pair formed in a rate-limiting process that is not acid catalyzed. In the absence of acid, the *N*-benzoylaziridines **2** of the present work are clearly more stable than the corresponding *N*-arylaziridines. This is consistent with the decreased availability in **2** of the nitrogen lone pair necessary for the stabilization of the postulated[6] imonium–carbonium ion intermediate. The same explanation has been used to account for the increased stability of certain nonbasic monochloroaziridines as compared to analogous 1-arylmonochloroaziridines.[8]

The observed requirement for acid catalysis in the methanolysis of the 1-benzoylaziridines **2** suggests initial protonation, presumably at the carbonyl oxygen atom as the most basic center in the molecule. Attack of chloride ion at C-2 of the resulting ion pair **13** (R′ = H) would give products of type **1** (*i.e.*, when R = alkyl). Similar nucleophilic attack by solvent would eventually lead to the amido esters of types **4** and **7**.



Methanolysis of the phenylaziridine **2b** presents a different picture. Ring rupture of **13** (R′ = H, R = C_6H_5) now involves the C-3–N bond, a cleavage mode that is common to the analogous 1,3-diaryl-2,2-dichloroaziridines.[5,6] Indeed, methanolysis of 1,3-diphenyl-2,2-dichloroaziridine also has been found to lead to **5** and **6** (in addition to aniline hydrochloride).[8]

The thermolytic rearrangement of the phenylaziridine **2b** is straightforward. In contrast to **2a** and **2c**, the phenyl substituent in **2b** labilizes the C-3–N bond and transformation to oxazoline **14** occurs. This type of rearrangement is common to many 1-acylaziridines,[10] but in the present case further elimination of HCl takes place to give the oxazole **8**. In this respect the reaction is analogous to the rearrangement of 1-benzoyl-3-chloro-2-methyl-3-phenylaziridine to 2,5-diphenyl-4-methyloxazole, reported by Fowler and Hassner.[7]

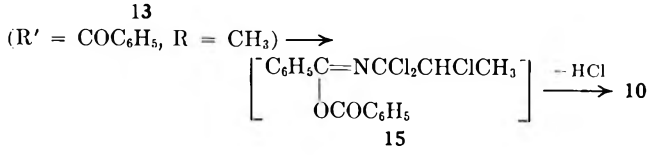


The formation of the imidate ester **10** from **2a** provides support for the view that the carbonyl oxygen

(9) E. Fischer, *Ber.*, **29**, 205 (1896).

(10) H. W. Heine and M. S. Kaplan, *J. Org. Chem.*, **32**, 3069 (1967), and references cited therein.

atom in 2 constitutes the most vulnerable site for initial attack on this relatively stable system. A likely mechanism for this process involves initial benzoylation (by benzoyl chloride formed as a decomposition product in the thermal process) to the ion pair **13** (R′ = COC_6H_5, R = CH_3). Chloride ion attack at C-3 with C-3–N bond rupture would give **15**, from which **10** would form by HCl elimination. Why C-2–N bond cleavage should occur in **13** (R′ = H, R = CH_3) and C-3–N bond rupture in **13** (R′ = COC_6H_5, R = CH_3), however, is not readily apparent.



Experimental Section

α-(1-Benzoyl-2,2-dichloro-3-aziridinyl)isobutyraldehyde (2c).—To a stirred suspension of 2.9 g (0.12 mol) of sodium hydride (washed free of mineral oil dispersant using pentane) in dry dimethylformamide (100 ml) was added a solution of **1c**[1] (18.5 g, 0.0575 mol) in dimethylformamide (50 ml). The addition rate was adjusted to maintain a temperature of 35° and the mixture was then stirred overnight at room temperature. The solution was separated from unreacted sodium hydride by centrifugation. The hydride was washed by centrifugation twice with dimethylformamide and once with benzene. The combined decantates were then concentrated to dryness under reduced pressure at a maximum temperature of 50°. The semisolid residue was partitioned between water and ether. From the ether layer, after washing, drying, and concentrating, was obtained 13.7 g of an amber oil. All but 2.6 g of this material dissolved in 250–300 ml of boiling pentane. This solution was decolorized with charcoal, concentrated to 75–100 ml, and allowed to stand at room temperature overnight in an open conical flask. The residual waxy solid (9 g) was slurried in pentane and filtered to give **2c** (7.5 g, 45%), mp 57–60°, sufficiently pure for further use. Two recrystallizations from pentane gave pure **2c**: mp 64–65°; ir ($CHCl_3$) 1690 (amide I) and 1720 cm^{-1} (HC=O), no NH; nmr ($CDCl_3$) δ 9.70 (s, 1, HCO), 8.3–7.6 (m, 5, Ar H), 3.23 (s, 1, NCH), 1.42 (s, 3, CH_3), and 1.37 ppm (s, 3, CH_3).

Anal. Calcd for $C_{13}H_{13}Cl_2NO_2$: C, 54.56; H, 4.58; Cl, 24.79; N, 4.90. Found: C, 54.86; H, 5.01; Cl, 24.46; N, 4.49.

The dichloroaziridine **2c** is thermally stable. It distilled at 140–145° (0.5 mm, bath temperature 215°) with only slight decomposition. When refluxed in xylene for 24 hr it could be recovered quantitatively.

When an equivalent rather than an excess of sodium hydride was used in the foregoing procedure the yield was reduced. When 1,2-dimethoxyethane was used as the solvent no **2c** could be isolated.

1-Benzoyl-2,2-dichloro-3-phenylaziridine (2b).—A solution of **1b**[1] (37.2 g, 0.113 mol, mp 172–173°) in dimethylformamide (200 ml) was added to a suspension of sodium hydride (4.9 g, 0.202 mol) in dimethylformamide as in the foregoing procedure. The mixture was then stirred at 40° for 5–6 hr and overnight at room temperature. The dark brown reaction mixture was poured onto ice. The precipitated amber-colored oil solidified, collected, and dried *in vacuo* at 45–50°. This crude product (27 g, mp 80–90°) was recrystallized once from methanol (200 ml + charcoal) to give 20.6 g (62%) of **2b**, mp 96–98°. Another recrystallization gave pure **2b**: mp 97–98°; ir ($CHCl_3$) 1700 cm^{-1} (amide I), no NH; nmr ($CDCl_3$) δ 8.5–7.5 (m, 10, Ar H) and 4.28 ppm (s, 1, NCH).

Anal. Calcd for $C_{15}H_{11}Cl_2NO$: C, 61.66; H, 3.80; Cl, 24.27; N, 4.80. Found: C, 61.78; H, 3.92; Cl, 24.58; N, 4.66.

When hexamethylphosphoramide was used as the solvent in the foregoing procedure, no **2b** could be isolated. When 3 equiv of 2,3-dimethyl-2-butene was added to a small run (2 g, 0.006 mol of **1b**), the yield of **2b** was reduced to 42%, but 36% of **1b** remained unreacted. When a volume of cyclohexane equal to that of the 2,3-dimethyl-2-butene was substituted for the latter, the yield of **2b** declined still further to 32%, and only 29% of **1b** remained.

1-Benzoyl-2,2-dichloro-3-methylaziridine (2a).—A solution of **1a**[1] (26.6 g, 0.1 mol, mp 111–112°) in dimethylformamide (120 ml) was added to a suspension of sodium hydride (4.32 g, 0.18 mol) in dimethylformamide as in the foregoing procedures. The mixture was stirred overnight at room temperature and then poured onto ice; the precipitated oil was taken up in ether, washed, and dried. The residual oil, obtained after removal of the ether, was distilled under reduced pressure to give 11.9 g (52%, $n^{25}D$ 1.549) of crude **2a**, bp 90–100° (0.8 mm). Redistillation gave pure **2a**: bp 87–89° (0.5 mm); $n^{25}D$ 1.5470; ir ($CDCl_3$) 1697 cm^{-1} (amide I), no NH; nmr ($CDCl_3$) δ 8.3–7.5 (m, 5, Ar H), 3.18 (q, 1, J = 6 Hz, NCH), and 1.53 ppm (d, 3, J = 6 Hz, CH_3).

Anal. Calcd for $C_{10}H_9Cl_2NO$: C, 52.20; H, 3.94; Cl, 30.82; N, 6.09; O, 6.96. Found: C, 52.00; H, 3.87; Cl, 30.57; N, 6.21; O, 7.23.

During 6 months at room temperature the analytical sample of **2a** gave off acidic fumes and became partially solid. Both ir and nmr spectra of this mixture showed that some of the trichloroamide **1a** had re-formed from the aziridine **2a**.

***N*-(2,2-Dichlorovinyl)benzamide (3d).**—*N*-(2,2,2-Trichloroethyl)benzamide (**1d**), mp 134–136°,[11] was prepared from chloral benzamide[12] by treating it with thionyl chloride and reducing the resulting *N*-(1,2,2,2-tetrachloroethyl)benzamide (without purification) to **1d** (87% yield) using sodium borohydride in ethylene glycol dimethyl ether (at 0–25°) followed by an equivalent quantity of triethylamine. To a stirred suspension of 1.1 g (0.045 mol) of sodium hydride in 1,2-dimethoxyethane (50 ml) was added at 20–25° a solution of **1d** (5 g, 0.02 mol) in 25 ml of the same solvent. The mixture was stirred at room temperature for 3 days, precipitated sodium chloride (1.52 g) was removed by filtration, and the filtrate was concentrated *in vacuo* to give a yellow oil (7.35 g) that slowly solidified. Trituration, successively, with water and chloroform gave **3d** (3.4 g, 79%), mp 61–63°, identical (mixture melting point and ir spectrum) with an authentic specimen, mp 63–64°, prepared by the method of Meldrum and Bhojraj.[13] When dimethylformamide was substituted for the dimethoxyethane in this procedure, only unreacted **1d** was obtained.

***N*-(2,2-Dichloro-1-styryl)benzamide (3b).**—A 6.57-g (0.02 mol) sample of **1b** was submitted to the foregoing procedure except that the reaction mixture was heated under reflux for 2 hr and stirred at room temperature overnight before work-up. The crude washed (water) product (4.9 g, 83%, mp 163–165°) was recrystallized from methanol to give pure **3b** (2.7 g, 46%): mp 173–174°; ir ($CHCl_3$) 1460 (amide II), 1680 (amide I), and 3410 cm^{-1} (NH). [For the known **3d**:[13] ir ($CHCl_3$) 1460 (amide II), 1689 (amide I), and 3420 cm^{-1} (NH). Furthermore, in both **3b** and **3d**, the amide II bands are (unusually) more intense than the corresponding amide I bands.]

Anal. Calcd for $C_{15}H_{11}Cl_2NO$: C, 61.66; H, 3.80; Cl, 24.27; N, 4.80. Found: C, 61.75; H, 4.05; Cl, 24.22; N, 4.56.

When the foregoing reaction was allowed to proceed for 8 days at room temperature, spectral (nmr) examination of the crude product indicated the presence only of **1b** (24%) and **3b** (76%). No aziridine **2b** was detectable.

***N*-(2,2-Dichloroisopropenyl)benzamide (3a).**—After treatment of **1a** (5.32 g, 0.02 mol) with sodium hydride in DME in the usual way, the mixture was heated under reflux for 6 hr. The crude washed product (3.4 g) was taken up in ether, decolorized with charcoal, filtered from some crystallized benzamide (0.39 g, mp 124–126°), and concentrated. The residual oil (2.27 g) was distilled under reduced pressure to give 1.23 g (27%) of an oil, bp 115–130° (0.5 mm), that partially solidified. Several recrystallizations from aqueous methanol gave pure **3a**: mp 100–102°; ir ($CHCl_3$) 1472 (amide II), 1685 (amide I), and 3420 cm^{-1} (NH); nmr ($CDCl_3$) δ 8.0–7.3 (m, 5, Ar H), 2.43 ppm (s, 3, CH_3).

Anal. Calcd for $C_{10}H_9Cl_2NO$: C, 52.20; H, 3.94; Cl, 30.82; N, 6.09. Found: C, 52.19; H, 3.87; Cl, 30.55; N, 6.17.

(11) A. N. Nesmeyanov, L. I. Zakharkin, and R. H. Friedlina, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 841 (1958); *Chem. Abstr.*, **53**, 1111 (1959).

(12) F. Feist, *Ber.*, **45**, 945 (1912).

(13) A. N. Meldrum and M. G. Bhojraj, *J. Indian Chem. Soc.*, **13**, 185 (1936).

Methanolysis of 2a.—A solution of the dichloroaziridine **2a** (1.31 g, 0.0057 mol) in dry methanol (25 ml) containing 5% hydrogen chloride was allowed to stand at room temperature for 1 week. The solvent was removed by distillation under reduced pressure and the residual semisolid oil (1.53 g) was allowed to stand in dry ether for several days. The ether solution was filtered from insoluble material (0.05 g), decolorized, and concentrated to dryness. The residual oil (1.2 g) was combined with equivalent material (1.2 g) from another run, and distilled under reduced pressure to give a colorless glass [2.17 g, bp 130–140° (0.8 mm), $n^{25}D$ 1.545)] that could not be crystallized. It was taken up in ether, washed with dilute hydrochloric acid and water, and finally washed with aqueous sodium bicarbonate and water. Acidification of the bicarbonate extract gave no precipitate. The combined acid extract and washings were concentrated to dryness under reduced pressure. The residual colorless solid (0.31 g, 14%, mp 154–157°) on recrystallization from chloroform gave pure *N*-benzoyl-*dl*-alanine, mp 158–159°, identical (mixture melting point, ir and nmr spectra, and elemental analysis) with an authentic sample.

From the washed, dried, and concentrated ether layer was obtained an oil (1.6 g) that was triturated first with pentane and then with a mixture of isopropyl alcohol (60%) and water (40%). Crystalline product (0.40 g, 13%, mp 105–107°) separated and was recrystallized from more of the isopropyl alcohol–water mixture to give pure *N*-(1,1,1-trichloro-2-propyl)benzamide (**1a**, 0.32 g), mp 111–112°, identical (mixture melting point, ir and nmr spectra, and elemental analysis) with the authentic material.[1]

The original aqueous isopropyl alcohol filtrate was decolorized and taken to dryness under reduced pressure. The residue (0.75 g) solidified and was recrystallized from benzene–hexane to give crude *N*-benzoyl-*dl*-alanine methyl ester (**4**, 0.60 g, 25%, mp 75–80°). Another recrystallization gave pure **4**, mp 80–81°, identical (mixture melting point, ir and nmr spectra, and elemental analysis) with a true sample.

When the methanolysis was conducted at reflux temperature for 48 hr instead of at room temperature, a 23% yield of *dl*-alanine methyl ester hydrochloride could be isolated in addition to **1a** and **4**.

Methanolysis of 2b.—A solution of **2b** (2 g, 0.00685 mol) in methanolic hydrogen chloride (30 ml, 5%) was allowed to stand at room temperature for 6 days. The solvent was removed by distillation under reduced pressure and the residue was taken up in dry ether. Insoluble material was collected at the filter, washed with ether, and dried. It proved to be ammonium chloride (0.34 g, 93% yield). Concentration of the ethereal filtrate gave a residual oil (1.9 g) that was separated into three pure components using preparative glc. By comparison (nmr spectra and qualitative glc) with authentic samples, they proved to be methyl benzoate, methyl α-chlorophenylacetate (**5**), and methyl α-methoxyphenylacetate (**6**). The composition of the mixture using quantitative glc was 49% methyl benzoate, 35% **5**, and 16% **6**. From the integrals of the nmr spectrum of the same mixture the calculated percentages were 44, 35, and 21%, respectively, corresponding to yields (based on the 1.9 g of crude methanolysis product) of 90% methyl benzoate, 53% **5**, and 32% **6**.

Methanolysis of 2c.—A solution of **2c** (7.5 g, 0.0262 mol) in dry methanol (75 ml) was allowed to stand at room temperature for 7 weeks. The mixture became deep yellow and strongly acidic. It was concentrated to dryness under reduced pressure and the semisolid residue (7.5 g) was triturated with ethanol. Colorless solid (2.94 g, 43%, mp 156–158°) was collected at the filter and recrystallized from methanol to give pure **4-hydroxy-4-methoxy-2-benzamido-3,3-dimethylbutyric acid γ-lactone (7)**: mp 158–159°; ir ($CHCl_3$) 1668 (amide I), 1778 (lactone C=O), 2835 (OCH_3), 3370 and 3425 cm^{-1} (NH); nmr ($CDCl_3$) δ 8.0–7.3 (m, 5, Ar H), 6.77 (d, 1, J = 8 Hz, NH), 5.22 (d, 1, J = 8 Hz, NCH), 5.00 (s, 1, OCH), 3.57 (s, 3, OCH_3), 1.28 (s, 3, CCH_3), and 1.08 ppm (s, 3, CCH_3).

Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32; O, 24.31. Found: C, 63.68; H, 6.50; N, 5.33; O, 24.44.

Inhibition of Methanolysis by β-Pinene.—When each of the three aziridines **2** was allowed to stand for 1 week (at 25°) in methanol containing 5% of the acid trap, β-pinene, the solution remained neutral and the starting material was recovered unchanged (85–95% yield).

Thermolysis of 2b.—A solution of **2b** (5 g, 0.0171 mol) in xylene (30 ml) was heated under reflux overnight. The solvent was removed by distillation under reduced pressure and the residual solid (4.3 g) was recrystallized (charcoal) from methanol to give 4-chloro-2,5-diphenyloxazole (**8**, 3.55 g, 81%, mp 67–69°). Two more recrystallizations gave pure **8**: mp 69–70°; uv max (C_2H_5OH) 224 mμ (ϵ 16,600) and 307 (25,300).

Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.45; H, 3.94; Cl, 13.87; N, 5.48; O, 6.26. Found: C, 70.59; H, 4.06; Cl, 13.67; N, 5.31; O, 6.50.

Hydrogenolysis of 8 to 9.—A suspension of 5% palladium on charcoal in methanol (150 ml) was prehydrogenated, and the chlorooxazole **8** (0.05 g, 0.002 mol) together with triethylamine (0.28 ml) were added. Hydrogenation in a microscale apparatus was continued until no further pressure drop (41 to 27 psi) was detectable. The catalyst was removed by filtration, and the filtrate was concentrated to dryness under reduced pressure. The residual solid (0.55 g) was slurried in water and collected at the filter. The dried product (0.36 g, mp 69–70°) was recrystallized from ethanol to give pure 2,5-diphenyloxazole (**9**), mp 70–71°, identical (mixture melting point, elemental analysis, and ir spectrum) with a true specimen prepared by the method of Fischer.[9]

Thermolysis of 2a.—Over a period of several months five portions of **2a** (17.8 g, 0.077 mol total) were submitted to the thermolysis conditions described above for **2b**. In all cases evolution of hydrogen chloride occurred with considerable decomposition. The product obtained after removal of the xylene was separated from tar by dissolving it in ether, decolorizing the solution with charcoal, filtering, and concentrating to dryness. The residual yellow oil was then treated in a number of ways. These included column chromatography on silica gel (heptane–ethanol solvent) and solvent fractionation using ether, methanol, chloroform, and hexane at various times. Four crystalline compounds were isolated (not all from any single run). Three were easily identified as benzoic acid, benzamide, and the trichloromethyl compound **1a**, mp 111–112°. The fourth (total yield, less than 150 mg) was obtained in pure form (tlc) by recrystallization from methanol: mp 160–161°; uv max (C_2H_5OH) 241 mμ (ϵ 11,500); ir ($CHCl_3$) 1117, 1250 (benzoate C–O stretch), 1715 cm^{-1} (benzoate C=O), and no NH; nmr ($CDCl_3$) δ 8.0–7.4 (m, 10, Ar H) and 2.28 ppm (s, 3, $=CClCH_3$); mass spectrum m/e (rel intensity, assignment) 333.0326 [0.5, calcd for $C_{17}H_{13}Cl_2NO_2$ (10): 333.0322], 298.0645 (1.3; calcd for $C_6H_5C(OCOC_6H_5)=NC^+=CClCH_3$: 298.0634), 193.0309 (5, calcd for $C_6H_5CON=C=CClCH_3$: 193.0294), 105 (100, $C_6H_5CO^+$), 77 (92, $C_6H_5^+$).

Anal. Calcd for $C_{17}H_{13}Cl_2NO_2$: C, 61.10; H, 3.92; Cl, 21.22; N, 4.19; O, 9.57. Found: C, 60.93; H, 3.95; Cl, 21.30; N, 4.36; O, 9.54.

The presence of a benzoate group in this compound was established by refluxing (16 hr) a sample (46 mg) in methanol (1 ml) containing sodium methoxide (from 0.012 g of Na). Presence of methyl benzoate in the reaction mixture was established by odor, nmr spectrum, and qualitative glc comparison with the authentic material.

Considering the method of preparation, the foregoing physical and chemical properties of the unknown compound (mp 160–161°) can be accommodated by only three possible structures: either the cis or trans form of **10** (*O*-benzoyl-*N*-(1,2-dichloropropenyl)benzimidate), or the isomeric imidate **12**. The third possibility (*i.e.*, **12**) was ruled out by the following experiment.

Hydrolysis of 10.—A solution of the imidate **10** (0.30 g, 0.9 mmol) and concentrated hydrochloric acid (4 ml) in tetrahydrofuran (20 ml) was heated under reflux for 2 days. The colorless solution was concentrated to dryness, and finally under reduced pressure (<1 mm) at 100°. The semisolid residue was pressed on a clay plate to obtain friable solid (0.095 g, 46%) which was recrystallized once from an ether–pentane mixture to give pure ***N*-(1,2-dichloropropenyl)benzamide (11)**: mp 115–117°; ir ($CHCl_3$) 1500 (amide II), 1695 (amide I), 3420 cm^{-1} (NH); nmr ($CDCl_3$) δ 8.2–7.5 (m, 5, Ar H), and 2.33 ppm (s, 3, $=CCH_3$); mass spectrum m/e (rel intensity, assignment) 229.0067 [0.1, calcd for $C_{10}H_9Cl_2NO$ (**11**): 229.0060], 194 (19, $C_6H_5CONHC^+=CClCH_3$), 159 (3, $C_6H_5CONHC=CCH_3$), 105 (100, $C_6H_5CO^+$), 77 (81, $C_6H_5^+$).

Anal. Calcd for $C_{10}H_9Cl_2NO$: C, 52.20; H, 3.94; Cl, 30.82; N, 6.09. Found: C, 52.20; H, 4.03; Cl, 30.30; N, 6.17.

That this hydrolysis product **11** is isomeric with but different from **3a** rules out **12** as a possible structure for the pyrolysis product **10**.

Benzoylation of 2a.—A solution of **2a** (1 g, 0.00435 mol) and benzoyl chloride (1.4 g, 0.01 mol) in dry xylene (15 ml) was heated under reflux for 16 hr using a fiberglass heating mantle. The dark brown solution was diluted with benzene (10 ml), decolorized with charcoal, and concentrated to dryness in a rotating evaporator under reduced pressure. The residual yellow oil (1.8 g) partially crystallized. Trituration with cold dry ether and collection at the filter gave 0.47 g (32% yield) of product, mp 145–150°. Recrystallization from methanol gave pure **10** (0.35 g, mp 158–160°) identical with the material obtained from the pyrolysis of **2a**. From the ethereal filtrate there was obtained an oil (0.47 g) which gave a colorless fraction (0.17 g) soluble in warm pentane. This oil could not be crystallized despite indications of virtual homogeneity by tlc analysis. Although its infrared and mass spectra (M^+ = 333.0339; calcd for $C_{17}H_{13}Cl_2NO_2$: 333.0322) were nearly identical with the corresponding spectra of **10**, the CH_3 singlet in the nmr appeared at δ 2.13 ppm instead of at 2.28 ppm for compound **10**. Structure **12** for this oil was again ruled out by the following experiment.

Benzoylation of 3a.—Application of the foregoing procedure to 1.31 g (0.0057 mol) of **3a** gave a dark oil (1.8 g) that crystallized upon trituration with ether. Collection at the filter gave 1.05 g (mp 108–111°, 55% yield) of crude product. Several recrystallizations from methanol gave pure *O*-benzoyl-*N*-(2,2-dichloroisopropenyl)benzimidate (**12**): mp 111–113°; ir ($CHCl_3$) 1700 cm^{-1} (C=O), and no NH; nmr ($CDCl_3$) δ 8.3–7.3 (m, 10, ArH), and 2.13 ppm (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{13}Cl_2NO_2$: C, 61.10; H, 3.92; Cl, 21.22; N, 4.19. Found: C, 61.36; H, 3.73; Cl, 21.43; N, 4.30.

Two solvent systems were used in tlc analyses to compare the three isomeric compounds **12**, **10**, and the oil obtained along with **10**: methylene chloride–nitrobenzene, 6:1, R_f 0.76, 0.86, and 0.86, respectively; and carbon tetrachloride–nitrobenzene, 6:1, R_f 0.47, 0.54, and 0.57, respectively. Tlc analysis of a crude reaction mixture from the benzoylation of the aziridine **2a** showed no more than a trace of material of R_f corresponding to that of **12**.

Registry No.—**2a**, 29431-38-7; **2b**, 29431-39-8; **2c**, 29431-40-1; **3a**, 29431-41-2; **3b**, 29431-42-3; **3d**, 29431-43-4; **7**, 29431-44-5; **8**, 29431-45-6; **10**, 29431-46-7; **11**, 29431-47-8; **12**, 29431-48-9.

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An Oxygen-18 Study of the Reaction of *N*-Phenylmaleamic Acid with Acetic Anhydride[1,2]

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N-Phenylmaleamic acid **1** labeled in the carboxyl group was prepared by basic hydrolysis of *N*-phenylmaleisoimide. The dehydration of **1** with *N*,*N*′-dicyclohexylcarbodiimide gave *N*-phenylmaleisoimide and *N*,*N*′-dicyclohexylurea; each contained 50% of the original label. Dehydration of the carboxyl-labeled **1** with an acetic anhydride–sodium acetate mixture produced an isoimide–imide product mixture which contained 34% of the original label. Treatment of carboxyl-labeled **1** with acetic anhydride alone was followed by isolation of maleic anhydride (as *endo-cis*-norbornene-5,6-dicarboxylic acid monomethyl ester) and acetanilide. These products contained 94 and 4% of the original label, respectively. The results rule out two mechanisms for this transacylation reaction: (1) a bicyclo [3.2.1] rearrangement of the mixed anhydride of **1** and acetic acid to give maleic anhydride and acetanilide, and (2) the reaction of acetic acid with the isoimide to produce these products. Other mechanisms for the transacylation and dehydration reactions of *N*-phenylmaleamic acid with acetic anhydride are discussed.

In a previous study[4] of the reaction of *N*-arylmaleamic acids **1** with acetic anhydride at 75°, maleic anhydride **2** and acetanilides **3** were found as products along with *N*-arylmaleisoimides **4** and *N*-arylmaleimides **5**. When sodium acetate was added to the reaction mixture, the same four products were observed, but the yields of maleic anhydride and the acetanilides decreased and the yields of the dehydration products **4** and **5** were increased. Furthermore, the production of **2** and **3** was more important when substituents attached to the position para to the amide nitrogen were electron donating than when the substituents were electron withdrawing. These reactions are outlined in Scheme I.

In earlier work Kretov and Kul'chitskaya[5] had isolated acetanilides from similar reactions run at the temperature of refluxing acetic anhydride, and Roderick and Bhatia[6] reported that heptafluorobutyranilide and *p*-methoxyheptafluorobutyranilide were obtained from the reaction of heptafluorobutyric anhydride with *N*-phenylsuccinamic acid and with *N*-*p*-anisylsuccinamic acid.

The previous study of the rearrangement of *N*-arylmaleisoimides to *N*-arylmaleimides in acetic anhydride with and without sodium acetate showed that the formation of the acetanilides and maleic anhydride did not occur as a result of the reaction of the isoimide with the solvent during kinetic runs.[4] We have now found that a small amount of acetanilide (and presumably maleic anhydride) is formed during a longer exposure of *N*-phenylmaleisoimide to acetic anhydride containing 2% acetic acid and that the acetanilides are unstable to the reaction conditions and react slowly with the solvent to form products which have been identified by mass spectra and nmr as *N*,*N*-diacylanilines. Previous

(1) A portion of this work was presented at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, Organic Division Abstracts No. 136.

(2) A preliminary account of part of this work has appeared: C. K. Sauers, *Tetrahedron Lett.*, 1149 (1970).

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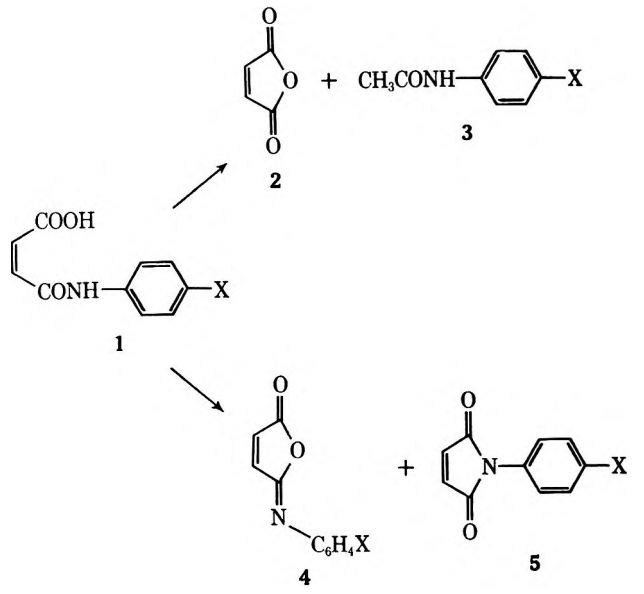
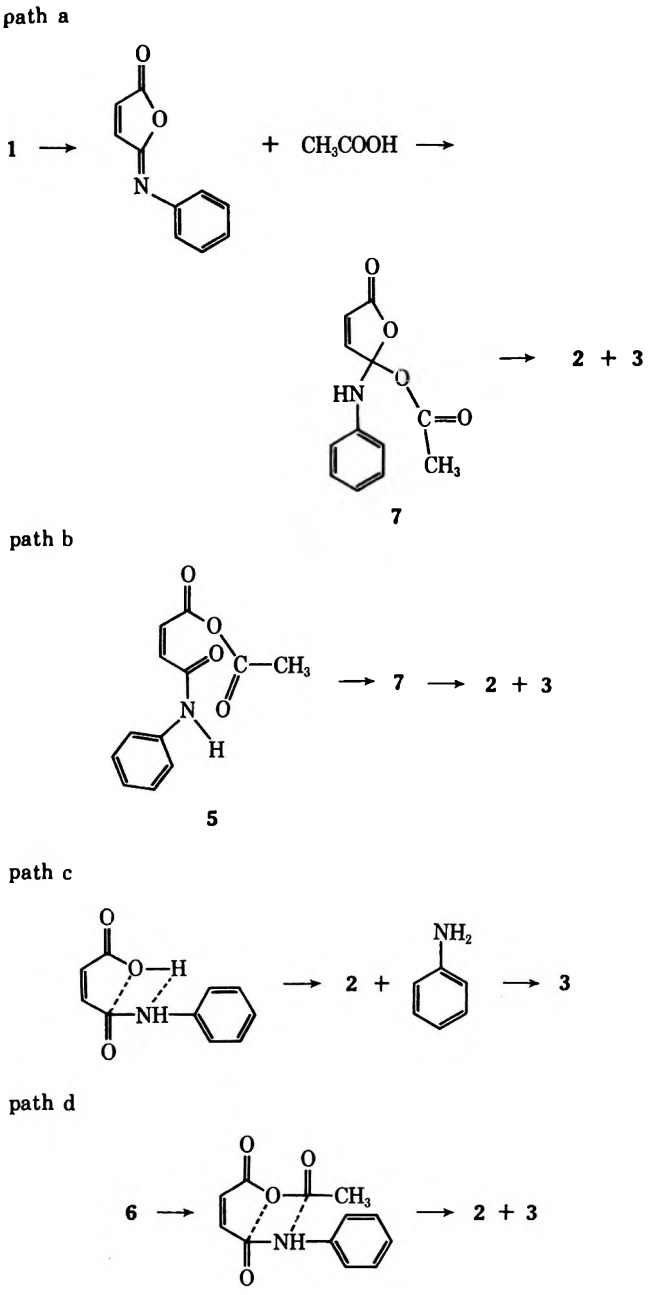
SCHEME I



SCHEME II



syntheses of these compounds involved more strenuous reaction conditions.[7-10]

A number of possible mechanisms may be suggested to account for the transacylation products, and these are outlined in Scheme II. The first process (path a) pictures the production of maleic anhydride and the acetanilides from a previously formed isoimide. The formation of the isoimides may occur by the loss of acetic acid from the mixed anhydride **6** formed by the reaction of acetic anhydride with the starting maleamic acid. Related mechanisms have been proposed for trifluoroacetic anhydride dehydration of amic acids,[6,11] and studies on the dehydration of amic acids with dicyclohexylcarbodiimide[12,13] support a similar mechanism for these reactions.

The addition of acetic acid to the carbon–nitrogen double bond to give a tetrahedral intermediate **7** which could collapse to anhydride and acetanilide is also analogous to reactions which have been previously reported. Thus, addition to the imino function of *N*-phenylphthalisoimide occurs with hydrazoic acid in chloroform[14] and during the acid-catalyzed hydrolysis of *N*-phenylmaleisoimide.[2] It is apparent from the very slow production of acetanilide from *N*-phenylmaleisoimide that this pathway cannot be a major one for this system.

Three additional mechanisms are possible to account for the transacylation reaction. Path b is analogous to the bicyclic mechanisms reported by Newman.[15] Path c is similar to the well-known catalysis of amide hydrolysis by neighboring carboxyl groups.[16] Other variations of path c are possible; *e.g.*, acylation at the nitrogen might take place before or during carboxyl participation. Path d combines features of path c with the suggestion by Roderick and Bhatia[6] that the transacylation reaction observed in the *N*-arylsuccinamic acid–heptafluorobutyric anhydride systems proceeds through a mixed anhydride intermediate.

Paths a and b may be differentiated from paths c and d by oxygen-18 labeling studies. In paths a and b one of the oxygens in the maleic anhydride product is derived from the acetic anhydride solvent. In contrast to this, paths c and d produce maleic anhydride composed of oxygens identical with those in the original maleamic acid. If the major source of the acetanilide

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and anhydride products were path a, then the anhydride would retain half the label and the acetanilide would be unlabeled. Furthermore, the collapse of **7** to acetanilide and maleic anhydride by a four-centered mechanism as in the third step of path b requires the carbonyl group of the acetanilide to have originated in the carboxyl group of the starting amic acid. In paths b and c the oxygen in the acetanilide carbonyl would be derived from the acetic anhydride.

These differences prompted us to synthesize *N*-phenylmaleamic acid labeled with oxygen-18. Labeled **1a** and **1b** (Scheme III) were prepared according to a procedure developed by Paul and Kende[13] for the synthesis of labeled *N*-*n*-butylmaleamic acid. *N*-Phenylmaleisoimide was treated with potassium hydroxide in water labeled with oxygen-18 and the location of the label in the *N*-phenylmaleamic acid product was determined by dehydrating this material with *N*,*N*′-dicyclohexylcarbodiimide. The oxygen-18 label was found to be equally distributed between the *N*,*N*′-dicyclohexylurea and the *N*-phenylmaleisoimide products. According to the mechanism of the carbodiimide dehydration reaction supported by the evidence of Kashelikar and Ressler[12] and Paul and Kende,[13] one of the carboxyl oxygen atoms would be removed during the reaction to become the carbonyl oxygen of the urea product. Therefore, the original maleamic acid produced by basic hydrolysis of the isoimide is labeled in the carboxyl group.

As we have previously reported,[2] hydrolysis of the *N*-phenylmaleisoimide under acidic conditions gives rise to a *N*-phenylmaleamic acid **1c** which is labeled primarily in the amide carbonyl oxygen. This conclusion arises from the observation that subsequent dehydration of **1c** with the carbodiimide reagent produces urea containing only 6% of the label and isoimide containing 94% of the label. These results were predicted by the kinetics of the hydrolysis of *N*-phenylphthalisoimide reported by Ernst and Schmir.[16e] Furthermore, it seems likely that hydrolysis of the isoimidium perchlorate salts derived from succinanilic acid[17] may proceed by attack of water at the immonium center.

A summary of the syntheses and dehydrations of the labeled *N*-phenylmaleamic acids is contained in Table I.

TABLE I

OXYGEN-18 ANALYSES[a] FOR THE SYNTHESIS OF *N*-PHENYLMALEAMIC ACID BY HYDROLYSIS OF *N*-PHENYLMALEISOIMIDE AND THE DEHYDRATION OF ACID BY *N*,*N*′-DICYCLOHEXYLCARBODIIMIDE

Hydrolysis conditions	Maleamic acid	Dehydration products	
		Isoimide	Urea
Basic	**1a**, 8.3 ± 0.2	4.2 ± 0.1	4.3 ± 0.0
Basic	**1b**, 1.33 ± 0.02	0.65 ± 0.03	
Acidic	**1c**, 7.9 ± 0.1	7.4 ± 0.1	0.5 ± 0.1
Neutral[b]	**1d**, 8.2 ± 0.1	6.5 ± 0.0	1.6 ± 0.1
Neutral[b]	**1e**, 3.2 ± 0.1		0.6 ± 0.0

[a] Average atom per cent excess oxygen-18 ± average deviation for two or more analyses. [b] The hydrolysis conditions were not neutral except at the start because the products, *N*-phenylmaleamic acid and phthalic acid, are acidic. (See Experimental Section.)

Included are the results of the hydrolysis of *N*-phenylmaleisoimide in oxygen-18 containing water with no added acid or base. These reactions have been discussed previously.[2]

The labeled maleamic acid **1b** was treated with acetic anhydride containing sodium acetate at 65° for a length of time sufficient to complete the formation of the imide and isoimide products. These were isolated from an aqueous sodium bicarbonate solution used to hydrolyze the acetic anhydride, and the isoimide–imide mixture was purified by column chromatography and analyzed for excess oxygen-18. Formation of these products by the internal displacement by the oxygen or nitrogen of the amide group of the acetate group of the mixed anhydride would require 50% of the label from **1b** to be found in the imide–isoimide product mixture. This percentage would not be altered by the isoimide–imide rearrangement which is known to occur under the reaction conditions[4] and which may occur under the work-up conditions[16e] since the oxygens of the imide formed in this way would be identical with the oxygens of the isoimide which rearranges.

However, analysis of the isoimide–imide product mixture showed that these compounds contained 34% of the label originally contained in the carboxyl group. The possibility that some of the label may have been lost in the work-up procedure through a reversible addition of water to the isoimide to form a symmetrical tetrahedral intermediate was considered. When a sample of unlabeled isoimide was dissolved in acetic anhydride and then reisolated by treatment of the mixture with sodium bicarbonate solution prepared from labeled water, no label was incorporated into the isoimide. This result indicates that a symmetrical tetrahedral intermediate is not formed reversibly under these conditions.

It is possible that the label in the mixed anhydride is distributed to all positions of the anhydride *via* pathways analogous to those proposed by Denney and Greenbaum for the reaction of aromatic anhydrides with ammonia and amines.[18]

N-Phenylmaleamic acid **1a** (labeled in the carboxyl group) was treated with acetic anhydride at 100°. Addition of cyclopentadiene followed by methanol produced a mixture of compounds containing only one acidic component (aside from acetic acid). This compound, the methyl half-ester of *cis-endo*-5,6-norbornenedicarboxylic acid **8a** was isolated by extraction with base, and acetanilide **3a** was separated from the mixture of neutral materials by column chromatography. These reactions and the accompanying oxygen-18 analyses are summarized in Scheme III.

Oxygen-18 analysis of purified **8a** and **3a** demonstrated that 94% of the label originally present in the carboxyl group was located in **8a** whereas only 4% was found in the acetanilide. The oxygen-18 data eliminate pathways a and b as mechanisms for the formation of acetanilide and maleic anhydride.

The fact that the reaction is more important in the absence of acetate ion is in accord with path c by analogy to the pH-rate profiles for phthalamic, maleamic, and substituted maleamic acids.[16,19] The reaction proceeds faster when the amic acid is derived from amines of greater basicity and this again supports

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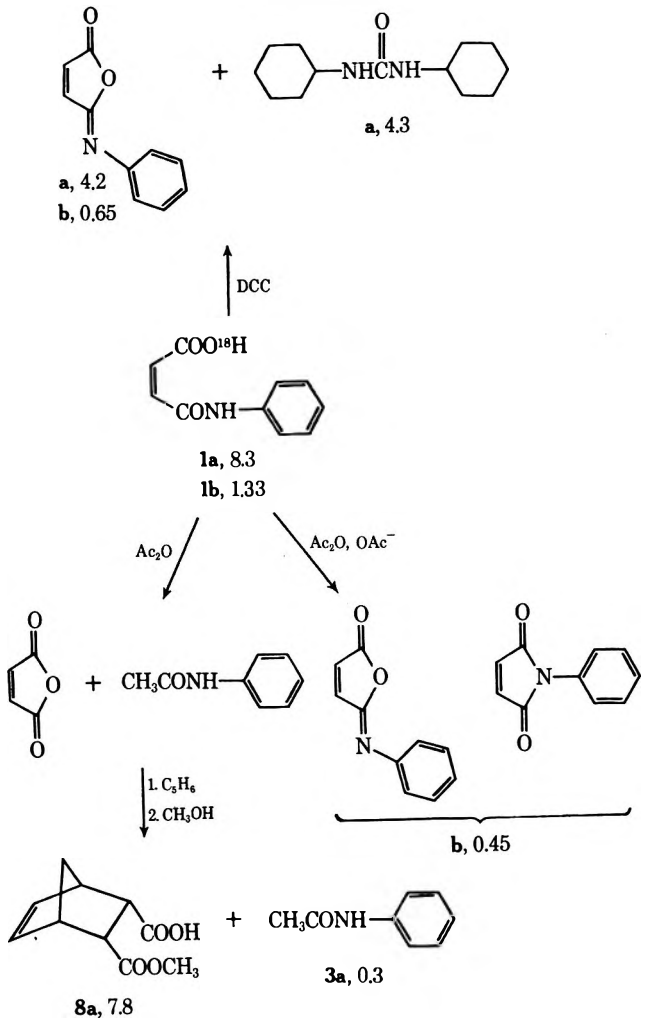
SCHEME III



path c by analogy to the observations of Dahlgren and Simmerman[16c] and Brown, Su, and Shafer[16d] on amic acid hydrolyses and Thanassi and Bruice on methyl hydrogen phthalate and chlorethyl hydrogen phthalate hydrolyses.[20] The high *isolated* yields of *N*-phenylphthalisoimmonium perchlorate obtained by Boyd[17] when the dehydrating reagent was acetic anhydride–perchloric acid suggest that the transacylation reaction is not taking place with this reagent. Since perchloric acid catalyzes a very rapid exchange reaction between acetic acid and acetic anhydride,[21] one would expect mixed anhydride formation to be very rapid with the acetic acid–perchloric acid reagent. For these reasons path c appears to be the most likely mechanism by which maleic anhydride and acetanilide are produced in these reactions, but path d or a combination of c and d cannot be unequivocally ruled out.

Experimental Section

Microanalyses were performed by George Robertson, Florham Park, N. J. Nuclear magnetic resonance spectra were run on a Varian A-60A spectrometer and infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer. Melting points are uncorrected.

Oxygen-18 Analyses.[22]—The method of analysis for oxygen-18 content was that of Rittenberg and Ponticorvo[23] modified by the use of an apparatus similar to that described by Williams and Hager.[24] Sealed sample tubes containing mercuric chloride or mercuric cyanide were heated in a furnace at 500° for 2–24 hr. This procedure was always carried out in a hood since hydrogen cyanide is a product of the combustion when mercuric cyanide is the catalyst. The resulting carbon dioxide was collected and sublimed in a vacuum line and introduced into a mass spectrometer. Samples derived from acids prepared with 10 atom % excess oxygen-18 water were analyzed on a Hitachi Perkin-Elmer Model RMU mass spectrometer.[25] The peak heights of peaks 44, 45, and 46 were measured to the nearest tenth of a millimeter and the atom per cent oxygen-18 was calculated from the formula

$$\% \text{ O-18} = \frac{\frac{1}{2}(46 \times 100)}{44 + 45 + 46}$$

Correction for the natural abundance of oxygen-18 was made by subtracting 0.20 from the value for per cent oxygen-18. This quantity was multiplied by the number of oxygen atoms in the molecule to obtain the values reported in Table I. Samples derived from acids prepared with 1.5 atom % excess oxygen-18 water were analyzed on a Consolidated-Nier Model 201 isotope ratio mass spectrometer.[26] The per cent oxygen-18 in the molecule was calculated from a modification of the formula published by Denney and Greenbaum[27]

$$\frac{[0.00408]46/44(\text{sample})}{46/44(\text{tank})} = \frac{2(0.98892)[Z(0.00204) + X] + 2(Z)(0.01108)(0.00037)}{0.98892[Z(0.99759) - X]}$$

where Z is the number of oxygen atoms in the molecule of the original sample and X is the atom fraction excess oxygen-18 per molecule.

Synthesis of Oxygen-18 Compounds.—*N*-Phenylmaleisoimide was prepared and purified by the dehydration of *N*-phenylmaleamic acid with *N*,*N*′-dicyclohexylcarbodiimide followed by chromatography on Florisil.[28] After drying it was stored in a tightly stoppered bottle in the refrigerator and used within 1 week of its preparation. Tetrahydrofuran was purified by distillation from lithium aluminum hydride immediately prior to each use. The labeled water was 10 atom % and 1.5 atom % purchased from Bio-Rad Laboratories.

Hydrolysis of *N*-Phenylmaleisoimide in $K^{18}OH$–$H_2{}^{18}O$.[2] Preparation of 1a and 1b.—A solution of 1.7311 g of *N*-phenylmaleisoimide in 3.75 g of dry tetrahydrofuran was added in one portion to a solution of potassium hydroxide in labeled water prepared by the addition of 1.4043 g of potassium *tert*-butoxide (obtained from MSA Research Corporation) to 2.3032 g of water containing 10 atom % oxygen-18. The exothermic reaction mixture was stirred in an ice bath for 12 min. After evaporation under reduced pressure, 2 ml of $H_2{}^{16}O$ was added and the mixture was acidified with concentrated hydrochloric acid. The product was collected by filtration and washed with water. *N*-phenylmaleamic acid 1a, an ivory powder having mp 197–199°, was isolated in 90% yield. Recrystallization from 80 ml of 95% ethanol yielded 70% purified 1a, mp 201–202°. Analysis for oxygen-18: 8.40, 8.13 atom % excess. A second preparation of this compound was carried out with 2.6287 g of *N*-phenylmaleisoimide, 8.4176 g of water containing 1.5% oxygen-18, 2.7190 g of potassium *tert*-butoxide, and about 3 ml of dry tetrahydrofuran. The product 1b was isolated as above except that concentrated sulfuric acid was used to precipitate the product. After recrystallization, 2.1886 g of *N*-phenylmaleamic acid 1b, mp 200–201.5°, was obtained. Analysis for oxygen-18: 1.35, 1.32, atom % excess.

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(25) We are indebted to Mrs. Van Es, School of Chemistry, Rutgers University, for obtaining these spectra.

(26) We are grateful to Professor Ernst Monse and Mr. Frank Torre, Rutgers University in Newark, for the use of this mass spectrometer.

(27) D. B. Denney and M. A. Greenbaum, *J. Amer. Chem. Soc.*, **79**, 979 (1957).

(28) R. J. Cotter, C. K. Sauers, and J. M. Whelan, *J. Org. Chem.*, **26**, 10 (1961).

Hydrolysis of *N*-Phenylmaleisoimide in H_2SO_4–$H_2{}^{18}O$.[2] Preparation of 1c.—A solution of 0.7822 g of *N*-phenylmaleisoimide in 4.0 ml of dry tetrahydrofuran was added over 30 sec to a solution of 0.1114 g of concentrated sulfuric acid in 1.0464 g of water containing 10 atom % oxygen-18. After 10 min the slurry was evaporated under reduced pressure and $H_2{}^{16}O$ was added to the pasty residue. The product, *N*-phenylmaleamic acid, was collected by filtration and washed five times with distilled water and dried, 0.6849 g (79%), mp 198–200°. After recrystallization from 35 ml of 95% ethanol, 513 mg (59%) of purified *N*-phenylmaleamic acid 1c was obtained, mp 201–202°. Oxygen-18 analysis: 7.96, 7.74, 8.04 atom % excess. A portion of this compound was subjected to the reaction conditions a second time in order to determine whether exchange of oxygen-18 in the molecule occurs during the reaction or work-up conditions. Thus 110 mg of 1c, 105 mg of concentrated sulfuric acid, 4 ml of tetrahydrofuran, and 1 ml of $H_2{}^{16}O$ were stirred for 10 min and worked up as before. The *N*-phenylmaleamic acid thus recovered weighed 41 mg. Analysis for oxygen-18: 7.96, 8.11 atom % excess.

Hydrolysis of *N*-Phenylmaleisoimide in $H_2{}^{18}O$. Preparation of 1d and 1e.—A clear solution of 245 mg of *N*-phenylmaleisoimide in 5.6 ml of water containing 10 atom % excess oxygen-18 and 1.970 g of tetrahydrofuran was allowed to stand at room temperature for 24 hr. Large crystals of *N*-phenylmaleamic acid 1d were deposited during this time. These were collected by filtration, the filtrate was evaporated under reduced pressure, and the residue was triturated with 95% ethanol and filtered. The combined precipitates were recrystallized from ethanol yielding 44 mg (16%) of a first crop and 25 mg (8%) of a second crop. Oxygen-18 analysis (first crop): 8.04, 8.28 excess atom %. Similarly a 213-mg sample of *N*-phenylmaleisoimide was added all at once to a mixture of 3.1071 g of $H_2{}^{16}O$ and 1.0307 g of $H_2{}^{18}O$ (containing 10 atom % oxygen-18). To this mixture was added 131 mg of Spectrograde acetonitrile. The pale yellow heterogeneous solution was stirred for 6 hr and then filtered, and the precipitate 1e (90 mg, 38%) was analyzed after drying under vacuum for 12 hr. Analysis for oxygen-18: 3.21 atom % excess. The remainder of the maleamic acid, 64 mg, was recrystallized from *ca.* 4 ml of 95% ethanol, yielding 43 mg of 1e. Analysis for oxygen-18: 3.27, 3.09 atom % excess. This reaction was repeated on a larger scale with unlabeled water. Thus 2 g of *N*-phenylmaleisoimide, 1.1 g of acetonitrile, and 40 ml of distilled water were stirred for 6 hr and the pH of the solution was monitored during this time. The pH fell rapidly to 4 and then slowly dropped to 2.8 at the end of the reaction. The product was isolated in the usual manner, 1.3 g (62%).

Dehydration of *N*-Phenylmaleamic Acid 1a–e with *N,N'*-Dicyclohexylcarbodiimide.—A slurry of 0.1493 g of *N*-phenylmaleamic acid 1a and 0.1683 g of *N,N'*-dicyclohexylcarbodiimide in *ca.* 8 ml of dichloromethane contained in a dry flask was stirred for 24 hr. *N,N'*-Dicyclohexylurea (0.1322 g, 82%) was isolated by filtration and purified by repeated washings with boiling dichloromethane. Analysis for oxygen-18: 4.27, 4.27 atom % excess. Similarly, 154 mg of 1b and 181 mg of the carbodiimide were stirred in dichloromethane and the urea and isoimide products were isolated and purified as above. The isoimide was analyzed. Oxygen-18: 0.63, 0.68 atom % excess. In a similar manner, 131 mg of 1c was treated with 160 mg of the carbodiimide. *N*-phenylmaleisoimide (56 mg, 46%) was isolated. Analysis for oxygen-18: 7.35, 7.45 atom % excess. The urea (119 mg, 84%) was obtained. Analysis for oxygen-18: 0.58, 0.43 atom % excess. Similarly *N*-phenylmaleamic acid 1d (32 mg) was treated with 33 mg of the carbodiimide, and the isoimide and urea products were isolated: isoimide, 11 mg (40%), analysis for oxygen-18, 6.52, 6.52 atom % excess; urea, 24 mg (69%), analysis for oxygen-18, 1.58, 1.45, 1.62 atom % excess. Similarly 1e (30 mg) and 34 mg of the dehydrating agent yielded 15 mg (47%) of the urea and 6.2 mg of the isoimide which was lost during the subsequent analysis. The urea, analysis for oxygen-18: 0.58, 0.64 atom % excess.

Transacylation Reaction of *N*-Phenylmaleamic Acid–$CO^{18}OH$ with Acetic Anhydride.—*N*-Phenylmaleamic acid 1a (0.3093 g, 0.00162 mol) was heated with 1.5 ml of freshly distilled acetic anhydride in a water bath at 100° for 10 min. The bright yellow reaction solution was cooled and treated with 1 ml of freshly distilled cyclopentadiene.[29] After the initial exothermic reaction had subsided, the reaction mixture was heated at 50° until the bright yellow color had faded. Methanol (50 ml) was added and the reaction mixture was heated at reflux for *ca.* 20 hr. The methanol was removed by distillation at atmospheric pressure. The residue, a deep red oil, was dissolved in about 60 ml of ether and this solution was washed twice with 50-ml portions of saturated sodium bicarbonate solution. The ether solution was used for the isolation of acetanilide. The bicarbonate solution was acidified with concentrated hydrochloric acid and was then extracted three times with ether. After drying (sodium sulfate) the ether was permitted to evaporate at atmospheric pressure. The clear red oil which resulted was triturated with pentane whereupon it slowly crystallized. Nmr indicated that the sample was contaminated with acetanilide (δ 2.17) and so it was redissolved in dichloromethane and extracted with three 30-ml portions of 0.1 *N* sodium hydroxide solution. The combined basic extracts were thoroughly washed with dichloromethane and then acidified with concentrated hydrochloric acid. The product was obtained by extraction with dichloromethane; the extract yielded 26 mg of *endo-cis*-norbornene-5,6-dicarboxylic acid monomethyl ester (8a). After recrystallization from ligroin (bp 65–85°) the sample (13 mg) was analyzed: 7.84 atom % excess oxygen-18. In an earlier reaction of acetic anhydride with 1a in which the acetanilide was not entirely removed from the maleic anhydride derivative, the excess oxygen-18 was found to be 7.20, 7.24 atom % excess.[30]

The original ether extract which contained neutral compounds was dried, evaporated, and then chromatographed on a 0.75 × 14 in. column of Florisil with benzene and mixtures of ether–benzene. Sixty 10-ml fractions were taken and three products were isolated. The first fractions (21–24) had mp 142–143°; nmr δ 7.3 (m, 5 H), 6.29 (2 H), 3.44 (4 H), 1.69 (m, 2 H), consistent with *cis-endo*-norbornene-5,6-dicarboxylic acid *N*-phenylimide (lit.[31] mp 144°). The second product (49–51) was acetanilide, mp 110–112.5° (lit.[32] mp 114°) The third product was obtained upon washing the column with ether, mp 133–136°. The nmr was consistent with that expected for the anilide of the ester–acid contaminated with acetanilide. Analysis for oxygen-18 in the acetanilide: 0.27, 0.28 atom % excess.

Reactions of Acetanilides with Acetic Anhydride.—During the course of a study of the reactions of *N*-para-substituted phenylphthalamic acids and maleamic acids with acetic anhydride,[32] it was noticed that the yields of *p*-chloroacetanilide as determined by gpc decreased after a short period and that a new product with retention time slightly less than that of *p*-chloroacetanilide appeared in the chromatogram (column, 5.5-ft 3% SE-30 on Varaport 30, 143°). Treatment of *N*-*p*-chloroaniline with a large excess of acetic anhydride at 65° for 24 hr followed by an aqueous sodium bicarbonate work-up and distillation produced *N,N*-diacetyl-*p*-chloroaniline: mp 64–66.5° (lit.[7] mp 66–67°); nmr (CH_2Cl_2) δ 7.43 (db, 2 H), 7.14 (db, 2 H, J = 8.5 Hz), 2.13 (s, 6 H); mass spectrum, molecular ion peaks 211 and 213, 3:1 ratio. This material had the same retention time as the material produced during the transacylation reaction above. *Anal.* Calcd for $C_{10}H_{10}O_2NCl$: C, 56.75; H, 4.76; N, 6.62. Found: C, 57.08; H, 4.96; N, 6.97.

Similarly *N,N*-diacetylaniline was prepared from aniline and was purified by distillation, bp 95° (6 mm) [lit.[8] bp 145–146° (13 mm)], and crystallized to a white solid: mp 31.5–35.5° (lit.[8] mp 37–37.5°); nmr (CH_2Cl_2) (7.3) (δ) (m, 5 H), 2.15 (s, 6 H).

In the same manner, *N,N*-diacetyl-*p*-toluidine was prepared and purified: bp 113° (6 mm) [lit. bp 160–161° (15 mm);[8] mp 48°[9]]; nmr (CH_2Cl_2) δ 7.28 (db, 2 H), 7.05 (db, 2 H, J = 8.5 Hz), 2.37 (s, 3 H), 2.22 (s, 6 H).

When *p*-anisidine was treated with acetic anhydride at 65° for 48 hr followed by an aqueous sodium bicarbonate work-up,

(29) L. F. Fieser, "Organic Experiments," D. C. Heath, Boston, Mass., 1964, p 83.

(30) During earlier work,[4] we isolated a sample which had mp 78–82°. Reexamination of the spectra for this sample reveals a small amount of contamination by acetanilide. M. S. Morgan, R. S. Tipson, A. Lowry, and W. E. Baldwin, *J. Amer. Chem. Soc.*, **66**, 404 (1944), report mp 76–78.5° while L. M. Rice and E. E. Reid, *ibid.*, **74**, 3955 (1952), report mp 101–102°. We have prepared authentic 8 by a reaction between methanol and *cis-endo*-norbornene-5,6-dicarboxylic anhydride which had mp 98–100°. An nmr of this substance containing 15% acetanilide was found to be identical with that of the unpurified 8a.

(31) J. R. A. Pollock and R. Stephens, Ed., "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965.

(32) C. K. Sauers, E. S. Ioannou, and C. L. Gould, unpublished work.

only *p*-methoxyacetanilide was obtained. The diacetyl derivative has previously been prepared by a similar reaction run at a higher temperature.[10]

Dehydration Reaction of *N*-Phenylmaleamic Acid $CO^{18}OH$ with Acetic Anhydride–Sodium Acetate.—*N*-Phenylmaleamic acid **1b** (0.4663 g, 0.00244 mol) was mixed with 0.5710 g of anhydrous sodium acetate and 10 ml of acetic anhydride. The mixture was heated at 65° for 90 min, then cooled, and slowly added to excess saturated sodium bicarbonate. The yellow precipitate which remained after the acetic anhydride had been hydrolyzed was filtered and dried. A benzene solution of this mixture was passed through a 2-in. column of Florisil in a Pasteur pipet and all of the yellow product was collected. After removal of the benzene at reduced pressure, the sample was dried *in vacuo* for 24 hr. An nmr ($CDCl_3$–TMS) indicated that the material was a mixture of imide and isoimide. Analysis for oxygen-18: 0.45, 0.45 atom % excess, 34% of the label found in **1b**.

Acetic anhydride (2 ml) was added to 0.157 g of *N*-phenylmaleisoimide; the resulting solution was poured into 18 ml of saturated sodium bicarbonate solution prepared from water containing 1.5 atom % oxygen-18. The mixture was stirred until the isoimide crystals could be isolated by filtration and purification was carried out as above. Analysis for oxygen-18: 0.00, 0.01 atom % excess.

Registry No.—*N*-Phenylmaleamic acid, 555-59-9; acetic anhydride, 108-24-7.

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Synthesis of D- and L-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid *via* Resolution

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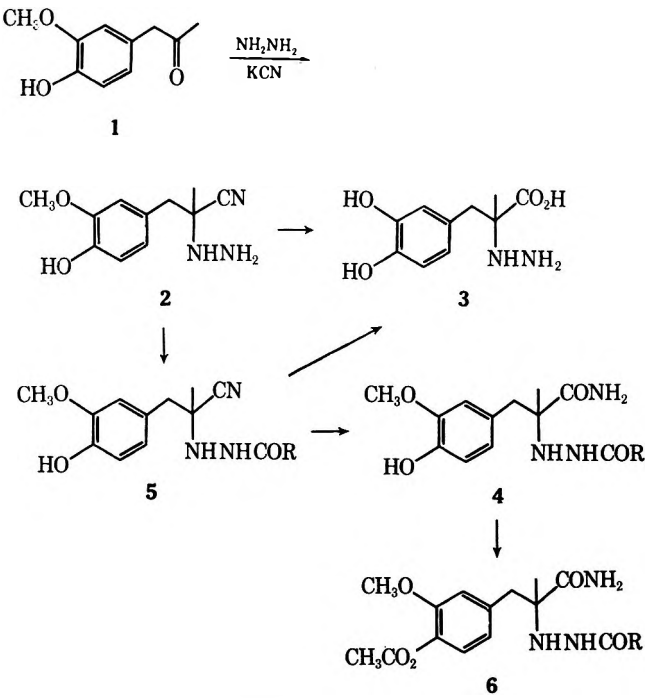
l-Menthoxyacetylation of *dl*-α-hydrazino-α-(4-hydroxy-3-methoxybenzyl)propionitrile (**2**) permits resolution and, after hydrolysis, the isolation of the two antipodes of α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid (**3**). The acylation is proven to have occurred on N^{β}.

In spite of seemingly increasing interest in the synthesis of α-hydrazinocarboxylic acids over the past decade,[1] only three methods are commonly used for their preparation. Two of these, the reduction of a hydrazone of an α-keto acid[1b] and the functionalization of a carbonyl compound in a Strecker-like synthesis,[2] are not particularly useful for the formation of optical isomers. The third, reaction of hydrazine with an α-halo acid, has so far proved to be the only useful route.[1a,b,3] Surprisingly, the resolution of racemic hydrazino acids by separation of diastereomers has yet to be reported.

The hydrazination reaction has severe limitations, especially in cases where the halogen to be replaced resides on a tertiary center and/or is ideally set up for base-promoted elimination as HX. Such a situation faced us in a projected preparation of the antipodes of α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid (**3**). Our interest in this work arose from the reported biological activity, both *in vitro*[4] and *in vivo*,[4,5] of the racemate[2] and the known "difference in biological activity associated with optical isomerism."[4b,6]

In this paper we report the first preparation of the antipodes of **3**[7] which was achieved by separation of diastereomeric hydrazides **5c** and by subsequent acid hydrolysis to the optically active hydrazino acids (**3**) (Scheme I). Inferences from the physical characteris-

SCHEME I



a, R = CH_3
b, R = C_6H_5
c, R = 1-menthoxymethyl

(1) For example, (a) A. Carmi, G. Pollak, and H. Yellin, *J. Org. Chem.*, **25**, 44 (1960); (b) E. J. Glamkowski, G. Gal, M. Sletzinger, C. C. Porter, and L. S. Watson, *J. Med. Chem.*, **10**, 852 (1967); (c) M. Sletzinger, R. A. Firestone, D. F. Reinhold, C. S. Rooney, and W. H. Nicholson, *ibid.*, **11**, 261 (1968), and references cited therein.

(2) M. Sletzinger, J. M. Chemerda, and F. W. Bollinger, *ibid.*, **6**, 101 (1963).

(3) A. Darapsky, *J. Prakt. Chem.*, **99**, 179 (1919); H. Niedrich and R. Grupe, *ibid.*, **27**, 108 (1965).

(4) (a) C. C. Porter, L. S. Watson, D. C. Titus, J. A. Totaro, and S. S. Byer, *Biochem. Pharmacol.*, **11**, 1067 (1962); (b) V. J. Lotti and C. C. Porter, *J. Pharmacol. Exp. Ther.*, **172**, 406 (1970).

(5) G. C. Cotzias, P. S. Papavasiliou, and R. Gellene, *New Engl. J. Med.*, **280**, 337 (1969), for example, report its usefulness in the treatment of Parkinsonism.

(6) A. H. Beckett, G. Kirk, and A. J. Sharpen, *Tetrahedron*, **21**, 1489 (1965).

(7) Attempts to resolve **2**, **3**, **4**, **5**, or **6** by separation of diastereomeric salts were thwarted by our inability to crystallize suitable salts with a variety of optically active acids.

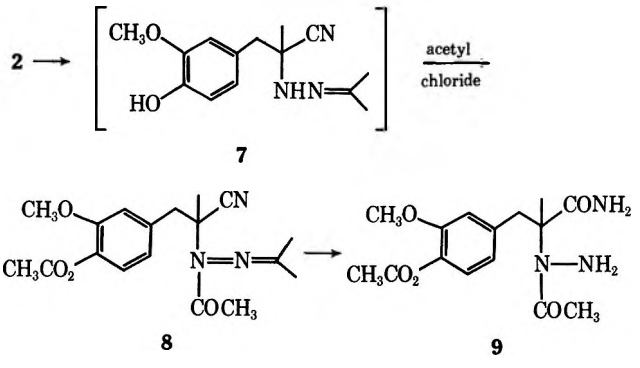
tics of the antipodes so obtained led us to the separation of racemic **3** by direct controlled crystallization. A following article[8a] deals with syntheses directly from optically active precursors, not involving attack at the asymmetric carbon atom. Therein also lies the proof of absolute configuration of C-2.[8b]

Hydrazinonitrile **2**, available *via* the synthesis of Sletzinger, Chemerda, and Bollinger,[2] could be selectively monoacylated with acetyl chloride or benzoyl chloride to give nicely crystalline hydrazides **5a** or **5b**. With l-menthoxyacetyl chloride, an oily mixture was ultimately induced to deposit crystals of mainly one diastereomer of **5c**. Subsequent preparations, when seeded, crystallized readily. After purification to constant rotation, the hydrazide could be hydrolyzed to levorotatory[8b] hydrazino acid **3**. Evidence of essential optical purity rests on rotational data of samples prepared from optically pure precursors[8a] and the achievement of constant rotation by repeated recrystallization.

Qualitative tests readily showed that L(−)-hydrazino acid **3** was less soluble than the racemic product. Accordingly, the mother liquor residues from the crystallization of L-hydrazide **5c** from which we could not crystallize its more soluble isomer were hydrolyzed. Several recrystallizations of the crude hydrazino acid obtained therefrom gave dextrorotatory **3**.

While simple aliphatic hydrazines are normally acylated on the substituted nitrogen, steric effects are frequently controlling.[9] Thus, it could be assumed that the acyl hydrazides **5a–c** were N^{β}-substituted, as depicted on Scheme I. Proof for this assumption came from the route shown in Scheme II. Reaction of ace-

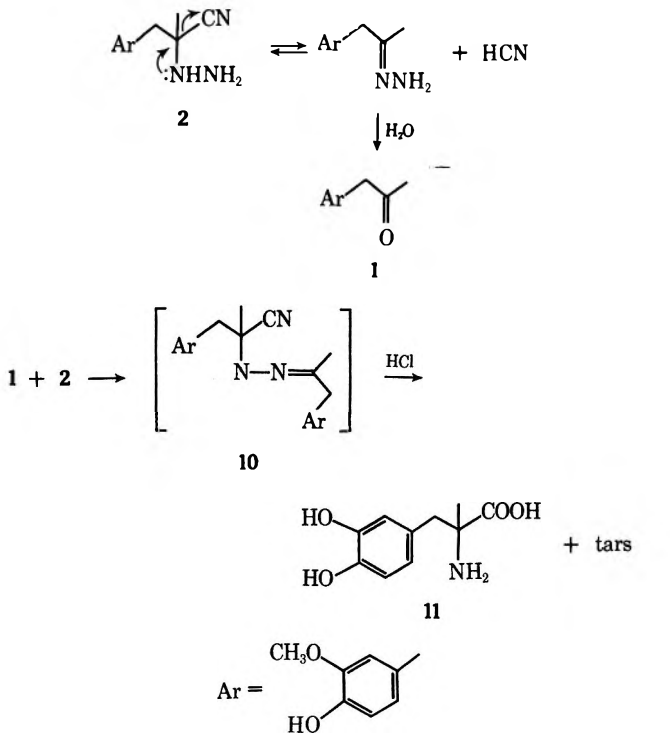
SCHEME II



tone hydrazone **7** with acetyl chloride gave the N^{α},O-diacetyl hydrazone **8**. Removal of acetone and concomitant hydration of the nitrile moiety gave **9** which was distinctly different from its positional isomer **6a** (Scheme I).

A novel N–N bond cleavage was observed during the study of the hydrolysis reaction **2** → **3**. It was noted that this reaction always produced some α-methyl-dopa (**11**) along with the desired hydrazino acid **3**. The amount of **11** produced was inversely related to the acid concentration of the medium. A likely pathway to explain these facts is depicted in Scheme III.

SCHEME III



Support for this scheme rests upon the observations that (a) hydrazino nitrile **2** readily loses hydrogen cyanide, even from the dry state, and such a dissociation could be expected to be repressed by strong protonation; (b) methyl vanillyl ketone **1** readily reacts with **2**, and the only product isolable from acid hydrolysis of an equimolar mixture of the two is α-methyl-dopa (**11**).

Resolution of *dl*-**3** *via* controlled direct crystallization (without resort to diastereomer formation) seemed likely, in view of the above-mentioned solubility relationships and X-ray evidence that the racemate was a mixture, not a compound.[10] Such a method, seldom used in the laboratory,[11] is uniquely useful, especially when large samples are required. A glassware bench-scale unit[12] similar in essentials to the commercial system already described[13] was set up and operated continuously in order to produce several hundred grams of each isomer.

Experimental Section[14]

α-(Acetylhydrazo)-α-(4-hydroxy-3-methoxybenzyl)propionitrile (5a).—To a cooled solution of hydrazinonitrile[2] **2** (2.21 g, 10 mmol) and triethylamine (1.4 ml, 10 mmol) in 25 ml of tetrahydrofuran and 35 ml of dioxane was added 1.1 ml of acetic anhydride. The mixture was stirred at room temperature

(8) (a) S. Karady, M. G. Ly, S. H. Pines, and M. Sletzinger, *J. Org. Chem.*, **36**, 1949 (1971). (b) Levorotatory **3** possesses L (*S*) configuration.[8a]

(9) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966, pp 127–128.

(10) This feature is not a requirement, but it appears helpful. For a comprehensive review of the methods of direct resolution, see R. M. Secor, *Chem. Rev.*, **63**, 297 (1963).

(11) For an example of its application, see H. E. Zaugg, *J. Amer. Chem. Soc.*, **77**, 2910 (1955), who resolved *dl*-methadone in like fashion.

(12) Unpublished work of Messrs. J. Allegretti, J. Meyer, and A. Wildman of the Chemical Engineering Research Staff of these laboratories.

(13) *Chem. Eng.*, **72**, 247 (1965).

(14) Melting points are uncorrected. Elemental analyses were performed by Mr. R. N. Boos and associates of these laboratories. Ir spectra were obtained with a Perkin-Elmer Model 137 Infracord, uv with a Perkin-Elmer Model 202 spectrophotometer, and nmr with a Varian A-60A. In the interests of brevity, ir, uv, and nmr data are not routinely reported. Unless otherwise stated, it may be assumed that all organic solutions were dried over sodium sulfate; solvent was removed by vacuum evaporation in a rotating evaporator. Preparative chromatographies were run on silica gel H (E. Merck). Commercially available tlc plates (Analtech or Brinkmann) were used without pretreatment.

for 1 hr and then evaporated to dryness. The resulting syrup was triturated with ether to afford 2 g (77%) of crystalline product. Recrystallization from ethyl acetate yielded analytically pure hydrazide **5a**, mp 123–124°.

Anal. Calcd for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.61; H, 6.63; N, 15.89.

α-(Benzoylhydrazo)-α-(4-hydroxy-3-methoxybenzyl)propionitrile (5b).—A solution of hydrazinonitrile **2** (2.21 g, 10 mmol) and triethylamine (1.4 ml, 10 mmol) in a mixture of tetrahydrofuran (25 ml) and dioxane (25 ml) was cooled rapidly (ice bath) and benzoyl chloride (1.16 ml, 10 mmol) was added rapidly. After a few minutes, the mixture was warmed to room temperature and stirred for 1 hr. The solvent was removed, and the residue was partitioned between ethyl acetate and sodium bicarbonate solution. The organic layer was washed with saturated sodium chloride solution, dried, and evaporated to dryness. Crystallization from chloroform and ether afforded 3 g of crystalline benzoyl hydrazide **5b**. An analytical sample was recrystallized from ethyl acetate, mp 135–136°.

Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 66.44; H, 5.89; N, 12.92. Found: C, 66.53; H, 6.03; N, 12.99.

α-(1-Methoxyacetylhydrazo)-α-(4-hydroxy-3-methoxybenzyl)propionitrile. 5c Resolution.—From similar reaction of 92.3 g of **2** and 1 equiv of 1-menthoxyacetyl chloride was isolated 66 g of crystalline product and a mother liquor residue A amounting to 130 g of syrup. The former was recrystallized to constant rotation to provide 12 g of pure **5c**, mp 126–126.5°, $[\alpha]_{546}$ −47.1° (*c* 0.8, MeOH).

Anal. Calcd for $C_{23}H_{35}N_3O_4$: C, 66.16; H, 8.45; N, 10.06. Found: C, 66.21; H, 8.68; N, 10.23.

L-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid (L-3).—A mixture of 25 ml of methanol and 30 ml of concentrated HCl was saturated at 0–5° with hydrogen chloride. To it was added 3 g of L-**5c** and the mixture was stirred overnight, warming to room temperature. The solvent was removed and replaced with 45 ml concentrated HCl and 5 ml acetic acid, and the solution was heated in a sealed tube at 120° for 90 min. After cooling, the contents were evaporated to dryness, taken up in 25 ml of ethanol, and precipitated by the addition of 5 ml of benzene and diethylamine to pH 6.5. The product (1.1 g, 58%) was recrystallized from hot water (charcoal) to give 900 mg of pure L-hydrazino acid, mp 203–205° dec, $[\alpha]_D$ −17.3° (MeOH).

Anal. Calcd for $C_{10}H_{14}N_2O_4 \cdot H_2O$: C, 49.17; H, 6.60; N, 11.47. Found: C, 49.13; H, 6.74; N, 11.19.

D-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid (D-3).—Syrup A (20 g) (above, synthesis of **5c**) was treated with hydrochloric acid as in the case of the L isomer. The crude product gave, after two recrystallizations from water, 700 mg of analytically pure D-hydrazino acid, mp 205° dec, $[\alpha]_D$ +17° (MeOH).

Anal. Found: C, 49.15; H, 6.45; N, 11.18. Thermogravimetric analysis showed 7.4% weight loss (theory, 7.4% for monohydrate).

α-(Acetylhydrazo)-α-(4-hydroxy-3-methoxybenzyl)propionamide (4a).—Propionitrile **5a** (5 g) was dissolved in 10 ml of ice-cold concentrated HCl and allowed to stand overnight. The precipitated product was filtered and washed with cold water and ethanol to afford 5 g of the hydrochloride of **4a**, mp 215–217°. To the slurry of 5 g of this salt in 200 ml of methanol was added 5 ml of propylene oxide. After 15 min the homogeneous solution was evaporated to dryness. Pure propionamide **4a** was obtained by crystallization from acetonitrile, mp 154–156°.

Anal. Calcd for $C_{13}H_{19}N_3O_4$: C, 55.50; H, 6.81; N, 14.97. Found: C, 55.37; H, 6.68; N, 14.91.

α-(Acetylhydrazo)-α-(4-acetoxy-3-methoxybenzyl)propionamide (6a).—To an ice-cold slurry of **4a** hydrochloride (634 mg, 2 mmol) in water (10 ml) was added 0.75 ml of 8 *N* potassium hydroxide and 0.25 ml of acetic anhydride. The mixture was stirred for 2 hr and then evaporated to dryness. The residue was stirred in 10 ml of tetrahydrofran and 1 ml of propylene oxide for 1 hr. The insolubles were removed and the filtrate was concentrated to a small volume. The resulting mixture was chromatographed on silica gel H, utilizing a mixture of chloroform, hexane, and methanol (8:2:1.5) as eluent. The pure diacetate **6a** was crystallized from ethyl acetate, mp 120–125°.

Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00. Found: C, 55.76; H, 6.56; N, 12.76.

α-(1-Acetyl-2-isopropylidenehydrazino)-α-(4-acetoxy-3-methoxybenzyl)propionitrile (8).—Hydrazinonitrile **2** (4.29 g, 20 mmol) was dissolved in 50 ml of acetone and the solution was allowed to stand for 1 hr. The solvent was removed under vacuum at room temperature leaving hydrazone **7** as a syrup. To its solution in 50 ml of tetrahydrofuran and 10 ml of pyridine was added dropwise 7.1 ml of acetyl chloride. After standing at room temperature for 4 days, the reaction mixture was evaporated to dryness and partitioned between ether and 2.5 *N* HCl. The organic layer was washed with potassium bicarbonate solution, the solvent was removed, and 800 mg of product was crystallized from ether and hexane. An analytical sample was prepared by recrystallization from ethyl acetate, mp 150–153°.

Anal. Calcd for $C_{18}N_{23}N_3O_4$: C, 62.59; H, 6.71; N, 11.98; O, 18.53. Found: C, 62.76; H, 6.76; N, 12.17; O, 18.74.

α-(1-Acetylhydrazino)-α-(4-acetoxy-3-methoxybenzyl)propionamide (9).—Hydrazone **8** (350 mg) was dissolved in a mixture of 8 ml of methanol, 8 ml of water, and 2 ml of 2.5 *N* HCl with warming (30–40°). The mixture was allowed to stand at room temperature for 2 hr and then evaporated to a small volume. The product was extracted with ethyl acetate. The solution was washed (saturated bicarbonate solution), dried, and concentrated to a small volume, and the product was allowed to crystallize. Recrystallization from ethanol–ethyl acetate yielded analytically pure α-acetylhydrazide **9**, mp 170–172°. This material was clearly separable by tlc (benzene–acetone–acetic acid 50:50:2) from the isomeric β-hydrazide, **6a**.

Anal. Calcd for $C_{15}H_{21}N_3O_5$: C, 55.72; H, 6.55; N, 13.00; O, 24.74. Found: C, 55.53; H, 6.63; N, 12.65; O, 25.26.

α-Methyl-dopa (11) from Hydrazinonitrile 2.—To a solution of hydrazinonitrile **2** (1.1 g) in 25 ml of tetrahydrofuran was added methyl vanilyl ketone (**1**) (975 mg) and the mixture was allowed to stand at room temperature. After 30 min a tlc probe indicated that the two components reacted to form a new compound (presumably hydrazone **10**). After the solvent was removed the residue was dissolved in concentrated HCl and heated to 120° for 2 hr in a sealed tube. The solution was filtered, evaporated to dryness, and dissolved in water. Racemic α-methyl-dopa was precipitated from the solution with ammonia. After recrystallization this was identical with authentic specimens. In the crude hydrolysate, hydrazino acid **3** was not detectable.

Registry No.—D-**3**, 28875-92-5; L-**3**, 28860-95-9; **4a**, 28957-67-7; **4a** HCl, 28875-94-7; **5a**, 28875-95-8; **5b**, 28875-96-9; **5c**, 28875-97-0; **6a**, 28875-98-1; **8**, 28875-99-2; **9**, 28876-00-8.

Synthesis of L-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid from Optically Active Precursors by N-Homologization

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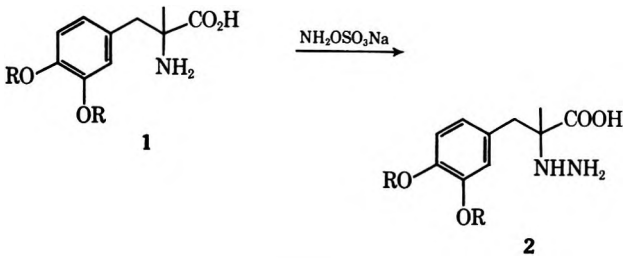
L-α-Methyl-dopa dimethyl ether (**1b**) reacts with hydroxylamine-*O*-sulfonic acid to give a difficultly separable mixture of **1b** and its N homolog, L-α-(3,4-dimethoxybenzyl)-α-hydrazinopropionic acid (**2b**). Reaction of the hydantoic acid **7b** with sodium hypochlorite also gives **2b**, easily isolable in this case. N-Amination of L-α-acetylamino-α-(3,4-dimethoxybenzyl)propionitrile *via* chloramine similarly provides access to the title compound. These reactions, achieved without disturbing the chiral carbon, constitute the first direct conversions of α-amino acids to α-hydrazino acids and formally interconnect the configuration of the two series of structures.

There were described in the preceding paper[1] two resolution routes to optically active α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid (**2a**), the L(−)[2] isomer of which possesses interesting physiological activity.[3] The ready availability of L(−)-α-methyldopa (**1a**)[4] and some of its derivatives[5] provided incentive for direct synthesis of this nitrogen homolog from optically active precursors. Such a synthesis would also constitute a formal proof of absolute configuration.[6]



1 **2**

a, R = H
b, R = CH_3

A search of the literature revealed no precedent for the direct conversion of α-amino acids to hydrazino acids.[7] It seemed likely, however, that some of the established methods for converting amines to hydrazines[8] might be utilized. In this paper we describe some successful studies along these lines.

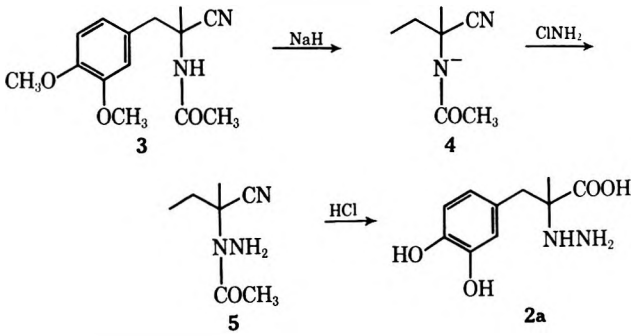
Substituted hydroxylamine derivatives have been used to form N–N bonds with amines.[9] Usually the amine is taken in excess to suppress secondary reaction of the reagent with the desired product. Purification, consequently, frequently presents problems. Nevertheless, we felt that, if reaction of commercially available hydroxylamine-*O*-sulfonic acid could be achieved with, for example, amino acid **1b**,[5b] this would constitute the simplest possible synthesis of hydrazino acid **2b**.

When such reaction was attempted in aqueous base, a mixture of starting material and product **2b** was obtained in 1.6:1 mole ratio. The reagent had been used in twofold excess, but neither increase nor decrease improved the yield. Separation of **1b** and **2b** was indeed difficult, and the approach was set aside as unsuitable for large-scale preparations.

It was clear that a more useful route would provide either complete conversion of starting material or at least a product which was readily separated from the starting material. The reactive anion **4** seemed a likely substrate on both counts, and its utility was examined. Optically active L-amide **3** had already been prepared,[5c] and its anion was shown to be optically stable under conditions deemed useful for our purposes.[10]

When this anion in DMSO was treated with ethereal chloramine,[11] smooth N-amination was achieved. The product, **5**, was readily convertible to the L-hydrazino acid **2a** by acid hydrolysis[1] (Scheme I).

SCHEME I



3 **4** **5** **2a**

Another hydrazine-forming reaction which seemed applicable to our goal was the interaction of urea with sodium hypochlorite.[12] Discovered in 1903, this reaction has rarely been used for the preparation of a substituted hydrazine. The transformation of amino acid **1** to hydrazino acid **2** based on this reaction is outlined in Scheme II.

The key intermediate, hydantoic acid **7b**, could be made from **1b** and potassium cyanate or from **7a**[5a] *via*

(1) S. Karady, M. G. Ly, S. H. Pines, and M. Sletzinger, *J. Org. Chem.*, **36**, 1946 (1971).

(2) Proof of absolute configuration follows.

(3) V. J. Lotti and C. C. Porter, *J. Pharmacol. Exp. Ther.*, **172**, 406 (1970).

(4) Aldomet, a product of Merck & Co., Inc.

(5) (a) R. A. Vitali, T. A. Jacob, and J. M. Chemerda, *J. Med. Chem.*, **7**, 379 (1964); (b) H. L. Slates, D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **29**, 1424 (1964); (c) D. F. Reinhold, R. A. Firestone, W. A. Gaines, J. M. Chemerda, and M. Sletzinger, *ibid.*, **33**, 1209 (1968).

(6) E. W. Tristram, J. ten Broeke, D. F. Reinhold, M. Sletzinger, and D. E. Williams, *ibid.*, **29**, 2053 (1964), have proven the configuration of L-α-methyl-dopa.

(7) Indirect syntheses *via* α-halo acids have been reported: (a) H. Niedrich and R. Grupe, *J. Prakt. Chem.*, **27**, 108 (1965); (b) M. Sletzinger, R. A. Firestone, D. F. Reinhold, C. S. Rooney, and W. H. Nicholson, *J. Med. Chem.*, **11**, 261 (1968).

(8) For a recent review, see A. N. Kost and R. S. Sagitullin, *Russ. Chem. Rev.*, **33**, 159 (1964).

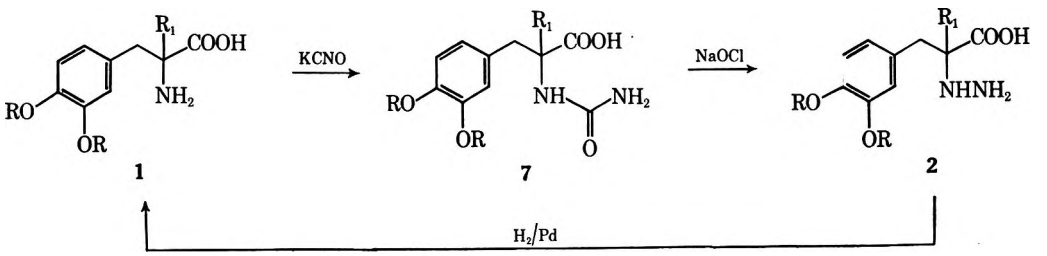
(9) For examples, see (a) L. A. Carpino, *J. Amer. Chem. Soc.*, **82**, 3133 (1960); *J. Org. Chem.*, **30**, 321 (1965); (b) T. Sheradsky, *Tetrahedron Lett.*, 1909 (1968), and subsequent papers from that laboratory.

(10) R. A. Firestone, D. F. Reinhold, W. A. Gaines, J. M. Chemerda, and M. Sletzinger, *J. Org. Chem.*, **33**, 1213 (1968).

(11) N-Amination of an amide anion has been reported by W. Metlesics, R. T. Travers, and L. H. Sternbach, *ibid.*, **30**, 1311 (1965).

(12) P. Shestakov, *Z. Angew. Chem.*, **16**, 1061 (1903).

SCHEME II

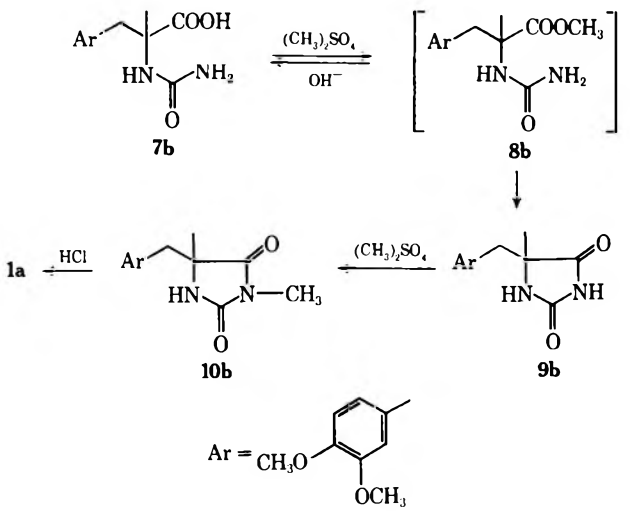


a, R = H; R_1 = CH_3
b, R = R_1 = CH_3
c, R = H; R_1 = Et
d, R = CH_3; R_1 = Et

methylation. Alternatively, α-methyl-dopa (**1a**) could be simply converted to **7b** in good yield without isolation of intermediate **7a**.

In the methylation step (**7a** → **7b**) methylhydantoin **10b** (Scheme III) formed as a by-product. Its yield

SCHEME III



was minimal when excess potassium hydroxide was used, but it increased when the pH was controlled at 11–12 during the reaction. Presumably hydantoic ester **8b** is the intermediate of this cyclization. At high base concentration, hydrolysis of the ester (**8b** → **7b**) is very rapid, while at lower base strength cyclization (**8b** → **9b**) becomes more competitive. Hydantoic ester **8b** could not be isolated. Even diazomethane converted **7b** to a mixture of hydantoins **9b** and **10b**, indicating rapid ring closure. Hydantoin **9b**, once formed, is expected to methylate at position 3 to give **10b**. Indeed, an authentic sample of hydantoin **9b** was readily transformed to **10b** by treatment with diazomethane or dimethyl sulfate. Hydrolysis of **10b** to α-methyl-dopa (**1a**) provided conclusive proof for the position of the *N*-methyl group.

The reaction of hydantoic acid **7b** with sodium hypochlorite gave hydrazino acid **2b** which was converted to the desired L-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid (**2a**) by treatment with hydrochloric acid (Scheme II).

An analogous sequence (**1c** → **7d** → **2d** → **2c**) provided L-α-(3,4-dihydroxybenzyl)-α-hydrazinobutyric acid (**2c**), the α-ethyl analog.

The outlined synthesis of levorotatory hydrazino acid **2a** from L(−)-α-methyl-dopa (**1a**) fixes the absolute configuration of the former as L or S.[6] As an additional proof, L-hydrazino acid **2b** was reconverted to the L-α-methyl-dopa analog **1b** by hydrogenolysis over palladium-on-charcoal catalyst (Scheme II).

Experimental Section[13]

Reaction of L-α-Amino-α-(3,4-dimethoxybenzyl)propionic Acid (1b) with Hydroxylamine-*O*-sulfonic Acid.—To an ice-cold solution of L-α-amino-α-(3,4-dimethoxybenzyl)propionic acid (**1b**) hydrochloride (2.2 g, 8 mmol) in 2.5 *N* NaOH was added 1.8 g (16 mmol) of hydroxylamine-*O*-sulfonic acid. After 10 min the mixture was warmed and kept at 90° for 1 hr. The solution was acidified with hydrochloric acid and evaporated to dryness *in vacuo*. The residue was digested with ethanol, and the product was precipitated from the alcoholic solution by the addition of diethylamine (pH 6.5). The crystalline product (900 mg) exhibited nmr resonances corresponding to **1b** and the desired hydrazino acid **2b** in a ratio of 1.6:1. (The C–CH_3 groups were sufficiently separated to allow this estimation.) Thin layer chromatography confirmed qualitatively these findings. For characterization of **2b**, see below.

L-α-(1-Acetylhydrazino)-α-(3,4-dimethoxybenzyl)propionitrile (5).—Sodium hydride (250 mg, 55% in mineral oil, 5.2 mmol) was washed with hexane and suspended in 6 ml of DMSO. To this mixture was added a solution of acetamidonitrile **3**[10] (1.05 g, 4 mmol) in 10 ml of DMSO. After the gas evolution subsided (15 min) the solution was cooled to 15°, and a solution of chloramine[14] (4.5 mmol) in 12 ml of dry ether was added over a period of 2 min. After 12 hr of agitation at room temperature, a few drops of acetic acid was added and the mixture was concentrated *in vacuo*. The resulting syrup was partitioned between water and chloroform. The organic layer was dried, the solvent removed, and the residue crystallized from ethyl acetate and ether to yield 1 g of crystalline material. The nmr spectrum indicated a 3:2 mixture of **5** and **3**. Chromatography on 30 g of silica gel H (chloroform–3% methanol) yielded 570 mg (52%) of **5** and 320 mg of recovered starting material. An analytical sample was prepared by recrystallization from methanol, mp 121–123°.

Anal. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.82; H, 7.10; N, 15.21.

L-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid (2a) from 5.—A solution of **5** (150 mg) in 2.5 ml of concentrated HCl was heated in a sealed tube at 120° for 90 min. After the usual work-up procedure (see **2b** → **2a**) 50 mg of pure hydrazino acid **2a** was obtained, identical in all respects with an authentic sample. For characterization of **2a**, see below.

L-4-(3,4-Dimethoxybenzyl)-4-methylhydantoic Acid (7b). A. From 1b.—L-α-Amino-α-(3,4-dimethoxybenzyl)propionic acid (**1b**) hydrochloride[5c] (44 g, 0.16 mol) was dissolved in 440 ml of water by gentle heating. The solution was cooled rapidly to 5°, and potassium cyanate (77.6 g, 0.96 mol) was added in small portions. After this the slurry was heated to 60° for 4 hr and filtered. The filtrate was cooled and acidified to pH 1 with

(13) For general comments see footnote 14 in ref 1.
(14) G. H. Coleman and H. L. Johnson, *Inorg. Syn.*, **1**, 59 (1939).

concentrated HCl, and the crystalline precipitate was filtered, washed with water, and dried at 50°, affording 34.5 g (76.4%) of hydantoic acid **7b**. An analytical sample was prepared by recrystallization from ethanol–water, mp 205–207°.

Anal. Calcd for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.56; H, 6.52; N, 9.99.

B. From L-α-Methyl-dopa (1a).—To a solution of L-α-methyl-dopa (100 g, 0.47 mol) and sodium bisulfite (600 mg) in 500 ml of water was added 57.6 g of potassium cyanate, and the solution was heated to 60° in a nitrogen atmosphere for 1 hr. Another 57.6-g portion of potassium cyanate was then added and the heating continued for 2 hr. An nmr study indicated that at this point about 90% of the amino acid was converted to hydantoic acid **7a**. This material was methylated without isolation as follows. Water was distilled from the reaction mixture until ammonia was no longer detectable. The residue was diluted to the original volume; 20 ml of 8 *N* KOH solution was added. The solution was well agitated while 8 *N* KOH solution (566 ml) and dimethyl sulfate (376 ml, 3.6 mol) were added simultaneously at such a rate as to keep the temperature below 20°. The addition took about 1 hr. The mixture was extracted with ether 0.5 hr later. The extract contained a small amount of dimethylhydantoin **10b** identical with a sample prepared by the methylation of hydantoin **9b** (see below).

The aqueous layer was acidified to pH 2 with HCl and the precipitated product was removed by filtration, washed with water, and dried to give 79 g (59%) of hydantoic acid **7b**.

When the methylation was carried out at pH 11–12, about 30% dimethylhydantoin **10b** formed, which was removed by filtration from the basic reaction mixture.

L-α-(3,4-Dimethoxybenzyl)-α-hydrazinopropionic Acid (2b).—To an ice-cold solution of hydantoic acid **7b** (2.2 g, 7.8 mmol) in 15.6 ml of 2.5 *N* KOH was added a solution of sodium hypochlorite (13.7 ml, 0.71 *N*, 9.75 mmol). Five minutes after the addition was completed, the solution was heated to 80° for 1.5 hr. After this period, toluene (45 ml) and hydrazine hydrate (0.8 ml) were added and the mixture was vigorously agitated while adding 8 ml of concentrated HCl. The mixture was stirred at 80° for 30 min; then the phases were separated and the aqueous layer was extracted with 25 ml of toluene. The toluene layer contained 3,4-dimethoxyphenylacetone and its condensation products. The aqueous layer was evaporated to dryness, and the resulting salt mixture was digested with ethanol. The alcoholic solution was neutralized (pH 6.4) with diethylamine and the precipitated product was filtered, washed with ethanol, and dried to afford 1 g of hydrazino acid **2b**, 48% yield. An analytical sample was recrystallized from water, mp 222–224° dec, $[\alpha]_D$ −9° (*c* 1, H_2O).

Anal. Calcd for $C_{12}H_{18}N_2O_4 \cdot H_2O$: C, 52.93; H, 7.40; N, 10.29. Found: C, 53.01; H, 7.46; N, 10.28.

A tlc and nmr study of the crude reaction mixture indicated that the major by-product of this reaction is hydantoin **10b**[5a] which formed in the basic medium. During the acidic work-up, more hydantoin formed from the unreacted hydantoic acid **7b**. This by-product was removed from the two-phase reaction mixture by filtration.

L-α-(3,4-Dihydroxybenzyl)-α-hydrazinopropionic Acid (2a).—A mixture of the dimethoxyhydrazino acid **2b** (10 g) and concentrated HCl (150 ml) was heated in a sealed tube at 120° for 2 hr. The reaction mixture was evaporated to dryness *in vacuo*, and the product was leached out with ethanol. The hydrazino acid was precipitated by the addition of diethylamine to pH 6.4. The precipitate was filtered, washed with ethanol, and dried, affording 6.5 g of hydrazino acid **2a** (73%). Recrystallization from water (containing a small amount of sodium bisulfite) yielded analytically pure material, mp 208° dec, identical with the material previously synthesized.

L-5-(3,4-Dimethoxybenzyl)-3,5-dimethylhydantoin (10b).—To a solution of hydantoin **9b** (1 g, 3.79 mmol) and potassium *tert*-butoxide (3.79 mmol) in 5 ml of DMSO, dimethyl sulfate (3.79 mmol) in DMSO (5 ml) was added dropwise. A few drops of acetic acid was added, and the mixture was evaporated under high vacuum. The residue was triturated with 2.5 *N* NaOH and filtered. Recrystallization from ethyl acetate yielded analytically pure **10b**, mp 153–155°.

Anal. Calcd for $C_{14}H_{18}N_2O_4$. C, 60.42; H, 6.52; N, 10.07. Found: C, 60.31; H, 6.60; N, 10.16.

α-Methyl-dopa from 10b.—L-5-(3,4-Dimethoxybenzyl)-3,5-dimethylhydantoin (**10b**) (5.87 g, 21 mmol) and 25 ml of 6 *N* HCl were heated in a sealed tube at 160° for 6 hr. The dark solution was evaporated to dryness, the residue was dissolved in water, and the α-methyl-dopa (**1a**, 2.9 g) was precipitated with ammonium hydroxide (pH 5). This material was identical in all respects with an authentic specimen.

α-Methyl-dopa Dimethyl Ether (1b) from 2b.—Hydrazino acid **2b** (2.08 g) in glacial acetic acid (100 ml) and 2.5 *N* HCl (3.2 ml) was hydrogenated in the presence of 10% palladium-on-charcoal catalyst (300 mg) for 24 hr at 120° and 40 psig. After the catalyst was removed the solution was evaporated to dryness and the residue was heated to reflux for 2 hr in concentrated HCl. The solution was treated with charcoal, concentrated to a small volume, and allowed to crystallize. The product (700 mg) after recrystallization from concentrated HCl had mp 164–171°, $[\alpha]_D$ 7.8° (*c* 1, MeOH).

Anal. Calcd for $C_{12}H_{18}ClNO_4 \cdot H_2O$: C, 49.02; H, 6.82; N, 4.72. Found: C, 48.75; H, 6.72; N, 4.74.

This material was identical in all respects with an authentic sample of α-methyl-dopa dimethyl ether hydrochloride hydrate, prepared by recrystallization of **1b** from concentrated HCl.

L-4-(3,4-Dimethoxybenzyl)-4-ethylhydantoic Acid (7d).—L-α-Ethyl-dopa **1c** was converted to the title compound **7d** in 70% yield by analogous procedure described above with the methyl analogs (**1a** → **7b**). The analytical sample was recrystallized from ethanol–water, mp 218–220°, $[\alpha]_D$ +241° (*c* 1, 2.5 *N* NaOH).

Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.74; N, 6.80; N, 9.45. Found: C, 56.71; H, 6.88; N, 9.53.

L-α-(3,4-Dimethoxybenzyl)-α-hydrazinobutyric Acid (2d).—Reaction with sodium hypochlorite converted hydantoic acid **7d** to hydrazino acid **2d** in 38% yield. The conditions were the same as outlined with the methyl analogs (**7b** → **2b**), mp 215–220°, $[\alpha]_D$ −7.3° (*c* 1, 2.5 *N* NaOH).

Anal. Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 58.16; H, 7.60; N, 10.40.

L-α-(3,4-Dihydroxybenzyl)-α-hydrazinobutyric Acid (2c).—The title compound was prepared from **2d** by the procedure outlined for **2a** in 90% yield. Recrystallization from water afforded an analytically pure sample, mp 209–212°, $[\alpha]_D$ −15.2° (*c*, 1, H_2O).

Anal. Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 55.02; H, 6.70; N, 11.65.

Registry No.—**1b** HCl, 5486-79-3; **2a**, 28860-95-9; **2b**, 28860-96-0; **2c**, 28860-97-1; **2d**, 28860-98-2; **5**, 28860-99-3; **7b**, 28861-00-9; **7d**, 28861-01-0; **10b**, 28861-02-1.

Synthesis and Reactions of 17β-Oxygenated 16α,17-Cyclopropylandrostanes

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Addition of carbene to the enol ether and enol acetate derivatives of several 17-keto steroids has provided the corresponding 16α,17-cyclopropyl steroids (**f**). The cyclopropyl ethers (**f**, R = Me, Et) on treatment with iodine afforded the *D*-homo unsaturated ketones (**e**) which may be alternately synthesized by base treatment of the keto aldehyde (**j**) resulting from ozonolysis of the Δ^{16}-17-methyl steroids (**k**). The cyclopropyl alcohol **1f** (R, R′ = H), formed by hydrolysis of its acetate, was readily isomerized with base to the corresponding *D*-homo ketone **1g** (R′ = H) or oxidized with, *e.g.*, ferric chloride, to a mixture of the unsaturated ketone **1e** (R′ = H) and the 16,17a-diketone (**1i**, R′ = H; Z = O). The addition of dibromocarbene to the enol ether gave the unsaturated bromo ketone **1h** (R′ = Ac; X = Br) which was also prepared by bromination of the cyclopropyl ether **1f** (R = Et; R′ = Ac). The dehydroacetoxylation of 5-acetoxyandrostanes on alumina is also described.

17-Methyltestosterone represents an early synthetic modification of testosterone which has enjoyed considerable utility in human therapy, largely due to its oral potency.[1] Since analogs of methyltestosterone with a larger 17α substituent exhibit in most cases a decreased physiological activity,[1] attention was turned to synthesis of compounds, the 16α,17-cyclopropyl derivatives, in which a sterically less bulky C-17α substituent was present.

Synthesis of the Cyclopropyl Ethers.—Initial plans for preparation of 16α,17-cyclopropyl steroids[2] involved reduction of the dihalocarbene adduct[3] formed from an enol derivative of a 17-keto steroid. Accordingly, the enol ether **1c** (R = Et; R′ = Ac), prepared from its ketal by elimination of ethanol in refluxing cymene, was treated with bromoform and potassium *tert*-butoxide. The product was the bromo unsaturated ketone **1h** (R′ = Ac; X = Br; λ_{max} 257 mμ), whose structure was consistent with mechanistic considerations,[3] the single vinyl proton in its nmr (438 Hz) and its elemental analysis. Further characterization was achieved by acid-catalyzed hydrolysis of its C_3-acetate group. Supporting evidence for the bromo unsaturated ketone structure came from its hydrogenation to the known *D*-homoandrostane **1g** (R′ = H).[4] Proof of structure of the bromo ketone **1h** (R′ = Ac; X = Br) was accomplished by an alternate synthesis involving addition of 1 mol equiv of bromine to the unsaturated ketone **1e** (R′ = Ac; see below) followed by dehydrobromination.

Attempts to isolate the dibromocyclopropane **1d** (R′ = Ac; X = Br), the logical intermediate to the unsaturated bromo ketone **1h** (R′ = Ac; X = Br), or to obtain evidence for its existence in the product (tlc, halogen analysis) were unsuccessful. A similar instability is displayed in simpler cyclopentene derivatives.[3] An attempt was made to prepare the analogous dichloro derivative **1d** (R′ = Ac; X = Cl) by treatment of the enol ether **1c** (R = Et; R′ = Ac) either with ethylene oxide–chloroform (essentially neutral conditions)[5] or with sodium trichloroacetate–sodium methoxide.[3] Although the dichloro adduct **1d** (R′ = Ac; X = Cl) was more stable than the bromo analog (as indicated by halogen analysis of the total reaction product), it was too unstable to isolate. The product isolated was the unsaturated chloro ketone **1h** (R′ = Ac; X = Cl) which had an ultraviolet spectrum with a maxium (243 mμ) displaced hypsochromically, as expected, from that of the corresponding bromo ketone. Hydrolysis of the 3-acetate group was again accomplished with acid. An immediate lithium–ammonia reduction of the freshly isolated dichlorocarbene reaction product yielded small amounts of the dehalogenated cyclopropyl derivative **1f** (R = Et; R′ = H); the chief product, however, was the saturated *D*-homo ketone **1g** (R′ = H), presumably formed by reduction of the unsaturated chloro ketone **1h** (R′ = H; X = Cl).

Direct addition of methylene to the enol ether was easily accomplished by use of diethylzinc and methylene iodide.[6] The product obtained from the enol ether **1c** (R = Et; R′ = Ac) was a new compound spectrally very similar to the starting material. Unambiguous evidence of the presence of the additional methylene group was obtained only from the mass spectral data (M^+ 312). Methylenation was similarly run on the enol methyl ether **1c** (R = Me; R′ = Ac), formed again by elimination of alcohol from its ketal. Both cyclopropyl derivatives **1f** (R = Me or Et; R′ = Ac) were transformed to their respective 3-hydroxy and then 3-keto derivatives by saponification followed by chromic acid oxidation (Scheme I). The nmr spectra of the latter clearly showed the cyclopropyl protons as multiplets at 40–50 Hz. The formation of the 16,17-cyclopropyl group is postulated to occur by α-face attack at the 16,17 double bond as has been documented for other reagents (*e.g.*, halogens, peracid).[7] Additional evidence of this cyclopropyl configuration is given below.

Reactions of the Cyclopropyl Ethers.—The cyclopropyl ethers were relatively stable to aqueous acid in refluxing methanol. Acetic acid solutions of *p*-toluensulfonic acid (at reflux) or hydrobromic acid (room temperature) produced mixtures of the *D*-homo

(1) P. D. Klimstra in "The Chemistry and Biochemistry of Steroids," Vol. 3, IntraScience Chemistry Reports, IntraScience Research Foundation, Santa Monica, Calif., 1969, p 83.

(2) A number of steroidal cyclopropanes have appeared in the recent literature. For examples, see J. Levisalles, G. Teutsch, and I. Tkatchenko, *Bull. Soc. Chim. Fr.*, 3194 (1969); D. E. Evans, G. S. Lewis, P. J. Palmer, and D. J. Weyell, *J. Chem. Soc.*, 1197 (1968); A. J. Birch and G. S. R. Subba Rao, *Tetrahedron, Suppl.*, **7**, 391 (1966).

(3) The addition of dihalocarbenes to enol ethers has been described, *e.g.*, by W. E. Parham, R. W. Soeder, J. R. Throckmorton, K. Kuncl, and R. M. Dodson, *J. Amer. Chem. Soc.*, **87**, 321 (1965). See also ref 13, p 160, and a recent review by R. Barlet and Y. Vo-Quang, *Bull. Soc. Chim. Fr.*, 3729 (1969).

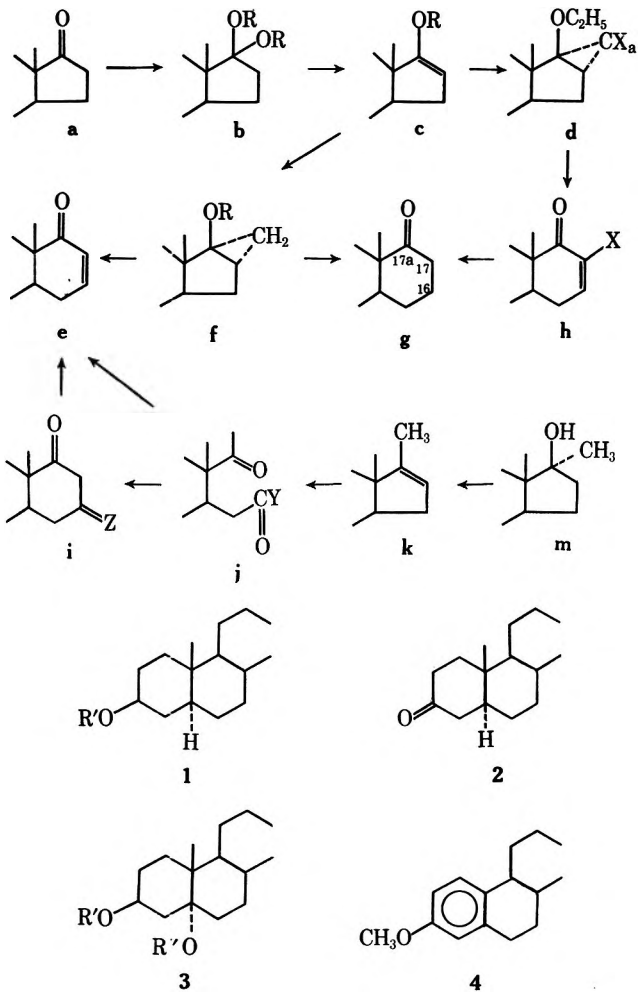
(4) A sample for comparison was prepared by hydrogenation of the Δ^5 derivative, in turn obtained by the synthesis of H. Heusser, P. Th. Herzig, A. Fürst, and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950), and kindly supplied by Dr. P. B. Sollman of these laboratories.

(5) F. Nerdel and J. Buddrus, *Tetrahedron Lett.*, 3585 (1965).

(6) J. Furukawa, N. Kabawata, and J. Nishimura, *Tetrahedron*, **24**, 53 (1968).

(7) See, *e.g.*, G. P. Mueller and W. F. Johns, *J. Org. Chem.*, **26**, 2403 (1961); N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Amer. Chem. Soc.*, **76**, 2943 (1954).

Scheme I



ketone **1g** (R′ = Ac) and additional products, probably 16-methylandrostan-17-ones (**1a**, 16-Me; R′ = Ac); with the latter reagent the mixture also contained brominated by-products.[8,9]

The ready reaction of the cyclopropyl ethers with halogens was first seen in an attempt to introduce a double bond into the A ring of the cyclopropyl derivative **2f** (R = Me); when direct dehydrogenation with dichlorodicyanoquinone or selenium dioxide proved unpromising, the A ring enol acetate of the ketone **2f** (R = Et) was brominated under neutral conditions. The resulting product, after magnesium oxide dehydrohalogenation, yielded an unsaturated D ring ketone (**e**) in which the A ring enol acetate was still intact. To further explore this reaction of bromine with the cyclopropyl ether grouping, the saturated 3-acetate **1f** (R = Me; R′ = Ac) was brominated and the resulting unstable product dehydrobrominated. The product was the *D*-homo unsaturated ketone **1e** (R′ = Ac) as suggested by its spectra and supported both by mechanistic considerations[8,9] and its facile hydrogenation to the known saturated ketone **1g** (R′ = Ac). Saponification of its 3-acetate followed by oxidation to the corresponding 3-ketone **2e** further characterized the product.

(8) A comparable example of a cyclopropyl ether cleavage has been described by E. Wenkert and D. A. Berger, *J. Amer. Chem. Soc.*, **89**, 2507 (1967).

(9) Other examples have been described by E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *ibid.*, **92**, 7428 (1970); R. E. Ireland, D. R. Marshall, and J. W. Tilley, *ibid.*, **92**, 4754 (1970).

The potential synthetic utility of this bromination reaction was limited by the rapid consumption of bromine in excess of 1 mol equiv, the excess resulting (after dehydrobromination) in formation of the unsaturated bromo ketone **1h** (R′ = Ac; X = Br). Iodine was seen to effect the same ring opening with minimal uptake of a second mole of halogen, thus giving a higher yield of the desired unsaturated ketone **1e** (R′ = Ac). The product was accompanied in this case by small amounts of the saturated *D*-homo ketone **1g** (R′ = Ac). In contrast to the cyclopropyl ether (**1f**, R = Et; R′ = Ac), the 17-acetate **1f** (R, R′ = Ac; see below) did not react with iodine.

A definitive structure proof of the unsaturated ketone **1e** was obtained by its synthesis from the ketoaldehyde **1j** (R′ = Ac; Y = H) *via* base-catalyzed cyclization.[10] The ketoaldehyde and the 17-ketone **1a** (R′ = Ac) were formed by direct ozonolysis of the olefin mixture resulting from phosphorous oxychloride dehydration of 17-methylandrostanediol 3-acetate (**1m**, R′ = Ac).

The same series of transformations were carried out for the Δ^4 ketone and the aromatic derivative **4k** yielding respectively the unsaturated ketones **2e** (Δ^4) and **4e**. In the latter case, mild base treatment of the ketoaldehyde **4j** afforded a crystalline ketol **4i** (Z = β-OH). The β configuration assigned to the 16-hydroxyl group was suggested by the relatively sharp nmr signal of its 16 proton. With more vigorous treatment this ketol dehydrated to provide the unsaturated ketone **4e**, which in turn was hydrogenated to the known *D*-homoestrone derivative **4g**.[11]

Insertion of the Δ^4 Bond.—Since preliminary investigations of direct insertion of an A ring double bond into the saturated 3-keto steroid **2f** (R′ = Me) had proved unsuccessful (see above), an alternate path was investigated starting with a 5-oxygenated androstane. The C-5 oxygen was expected to withstand the conditions of the carbene insertion sequence and could, at an appropriate time, be eliminated to form the desired unsaturation. (An unprotected double bond would be attacked by carbene.) Accordingly, 3β,5α-dihydroxyandrostan-17-one (**3a**, R, R′, R″ = H)[12] was treated with ethyl orthoformate to effect ketal formation. The instability of the molecule in this reaction was seen from the formation of the 5-dehydro derivative (as its 3-formate), the 3-monoformate of the starting diolone, and a number of less tractable derivatives. Ethyl orthoformate reacted smoothly with the 3,5-diacetate **3a** (R′, R″ = Ac), however, to yield the diethyl ketal **3b** (R = Et; R′, R″ = Ac). Recrystallization of this ketal from methanol converted it to the 17β-ethoxy-17α-methoxy ketal, the structure being suggested by the nmr spectra, the probable mechanism of the alcohol exchange, and conversion of the mixed ketal in boiling cymene to the enol *ethyl* ether. The enol ether **3c** (R = Et; R′, R″ = Ac), prepared from the diethyl ketal in hot cymene, was methylenated to provide 70% of the desired 16,17-cyclopropyl derivative **3f** (R = Et; R′, R″ = Ac) by direct crystallization. This compound was converted with lithium aluminum hydride to the 3,5-diol **3f** (R =

(10) For a similar synthesis of *D*-homo unsaturated ketones, see W. F. Johns, *J. Org. Chem.*, **26**, 4583 (1961).

(11) M. W. Goldberg and S. Studer, *Helv. Chim. Acta*, **24**, 295E (1941).

(12) K. I. H. Williams, R. S. Rosenfeld, M. Smulowitz, and D. K. Fukushima, *Steroids*, **1**, 377 (1963).

Et; R′, R″ = H) or with base to the 5-monoacetate. Chromic acid oxidation of the latter followed by base treatment yielded the 17-etherified testosterone analog **2f** (R = Et; Δ^4) in good yield.

Cyclopropyl Alcohol Synthesis and Reactions.—The 17-hydroxy-16α,17-cyclopropane derivatives were synthesized by addition of carbene to the androstane enol acetate **1c** (R, R′ = Ac). The product was a new compound **1f** (R, R′ = Ac) whose structure was again most clearly shown by the mass spectrum (M^+ 388) in conjunction with the general similarity of both its ir and nmr spectra to those of starting material. A lower yield of product and higher return of starting material reflected the decreased reactivity of the double bond, a result of the greater electron-withdrawing power of the acetate group as compared to the ether.[13] Lithium aluminum hydride reduction or careful alkaline hydrolysis converted the diacetate to the diol **1f** (R, R′ = H). This structure was supported by the dual method of preparation and by reacetylation of the diol to the starting diacetate.

The isomerization of the diol **1f** (R, R′ = H)[14] with potassium hydroxide in aqueous methanol at room temperature provided in high yield the *D*-homo ketone **1g** (R′ = H) mixed with minor amounts of the isomeric 16-methylandrostanes (**1a**, 16-Me; R′ = H; vpc analysis). With *p*-toluenesulfonic acid in aqueous methanol at reflux the initial product was a mixture of the *D*-homo ketone **1g** (R′ = H) and 3-hydroxy-16α-methylandrostan-17-one (**1a**, 16α-Me; R′ = H) in a 2:3 ratio. With prolonged acid treatment racemization of the 16-methyl group occurred. The cyclopropyl diol also isomerized upon chromatography (alumina or silica gel) or upon standing in chloroform solution giving mixtures of the same three products. The vpc identification of the 16α-methylandrostane **1a** (16α-Me; R′ = H) as the initial isomerization product of the cyclopropyldiol affords evidence that the cyclopropyl ring is on the α face of the molecule, a simple cleavage of the 16′,17 bond giving the 16α-Me group.

The diol **1f** (R, R′ = H) underwent ready oxidation with several oxidants, including chromic acid–pyridine, chromic acid–acetone, and *N*-bromoacetamide. These reagents effected oxidation at both C-3 and in the D ring, whereas milder oxidants, such as ferric chloride, caused reaction only in the latter.[15] The chief pathway of all of these oxidations involved transformation of the cyclopropyl alcohol into the readily identified *D*-homo unsaturated ketone (**e**). In addition, the *D*-homo ketone, a product of acid-catalyzed isomerization, was formed. Another component of the oxidation product was suggested by its uv spectrum to be the 16,17a-diketone **2i** (Z = O).[16] An alternate synthesis of this diketone was effected by ruthenium tetroxide oxidation of the olefin **1k** (R′ = Ac)[17] to afford the acid **1j** (R′ = Ac; Y = OH), followed by esterification and base-catalyzed cyclization. Oxidation of the 3-hydroxyl group gave the same trione **2i** (Z = O) as obtained from oxidation of the cyclopropyl alcohol **1f** (R, R′ = H).

Selective hydrolysis of the diacetate **1f** (R, R′ = Ac) was successfully accomplished with aqueous bicarbonate. The desired 3-monohydroxy compound **1f** (R = Ac; R′ = H) was accompanied by a varying amount of diol **1f** (R, R′ = H) and the *D*-homo ketone **1g** (R′ = H). Oxidation of the 17-mono ester gave the 3-ketone **2f** (R = Ac) and this in turn was hydrolyzed to the 17-hydroxy derivative **2f** (R = H).

Insertion of the A ring unsaturation was accomplished by use of the C-5 acetate as described above. The enol triacetate **3c** (R, R′, R″ = Ac) was methylenated to give the cyclopropyl triacetate **3f** (R, R′, R″ = Ac) which was reduced with lithium aluminum hydride to provide the cyclopropyl triol **3f** (R, R′, R″ = H). Base treatment of the triacetate (or the corresponding 3,17-diol) caused ready formation of the *D*-homo ketone **3g** (R′ = H; R″ = Ac); the latter was acetylated to give the diacetate **3g** (R′, R″ = Ac) and was also converted by chromic acid oxidation followed by base treatment to the known unsaturated ketone **2g** (Δ^4).[18]

Bicarbonate hydrolysis of the triacetate **3f** (R, R′, R″ = Ac) afforded, by direct crystallization, the 3,17-diol **3f** (R, R′ = H; R″ = Ac) whose structure was confirmed by reacetylation to the starting triacetate. The mother liquors of this hydrolysis were analyzed by chromatography on acid-washed alumina and provided the desired 3-monohydroxy diacetate **3f** (R′ = H; R, R″ = Ac), the starting triacetate, and the *D*-homo ketone **3g** (R′ = H; R″ = Ac). In a later repetition of this experiment, alkaline alumina was used for the chromatography and yielded, instead of the 5-acetoxy compounds, the corresponding Δ^5 derivative **1f** (R = Ac; R′ = H; Δ^5). The corresponding unsaturated ketone **2f** (R = Ac; Δ^4) was obtained either by Oppenauer oxidation of this olefin or by chromic acid oxidation of the monoalcohol **3f** (R′ = H; R, R″ = Ac) to its ketone followed by dehydroacetoxylation on alumina. Subsequent bicarbonate treatment afforded the testosterone derivative of **2f** (R = H; Δ^4).

The elimination of the 5-acetate group on alkaline alumina was also seen in the chromatography of the 17-ethoxy derivative **3f** (R = Et; R′ = H; R″ = Ac). Similar treatment of the 17-ketone **3a** (R′ = H; R″ = Ac) afforded dehydroepiandrosterone, some starting material, and *ca.* 5% of androstenedione. The latter probably arose as the result of a slow aluminum alkoxide oxidation of dehydroepiandrosterone in a reaction analogous to the Oppenauer oxidation. The reaction of the 3,5-diacetate **3a** (R′, R″ = Ac) on alumina provided the same products but at a much slower rate; absence of the 3-acetate Δ^5 derivative of **1a** (Δ^5; R′ = Ac) indicates that hydrolysis of the 3-acetate group occurs before elimination of the 5-acetate. The 3-hydroxy Δ^4 derivative was not seen in any of the dehydroacetoxylations.

Cyclopropyl Estratrienes.—Both the enol ethyl ether and enol acetate of estrone methyl ether were prepared and treated with diethylzinc–methylene iodide to

(13) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 29.

(14) For a review of cyclopropanol chemistry, see C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).

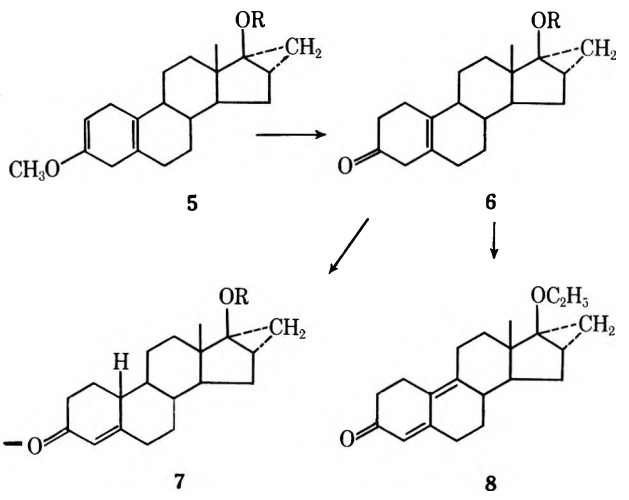
(15) Examples of cyclopropanol oxidation have been described by P. S. Venkataramani and W. Reusch, *Tetrahedron Lett.*, 5283 (1968), and S. E. Schaafsma, H. Steinberg, and Th. J. DeBoer, *Recl. Trav. Chim. Pays-Bas*, **85**, 73 (1966).

(16) For an alternate preparation of this material, see C. Thal and B. Gastambide, *Bull. Soc. Chim. Fr.*, 1222 (1966).

(17) F. Sondheimer, R. Mechoulam, and M. Sprecher, *Tetrahedron*, **20**, 2473 (1964); D. M. Piatak, H. B. Bhat, and E. Caspi, *J. Org. Chem.*, **34**, 112 (1969).

(18) M. W. Goldberg, J. Sice, H. Robert, and Pl. A. Plattner, *Helv. Chim. Acta*, **30**, 1441 (1947).

provide the corresponding cyclopropyl derivatives.[19] The ether **4f** (R = Et) was found to be stable to lithium–ammonia reduction, allowing preparation of the $\Delta^{5(10)}$- (**6**, R = Et) and Δ^{4}-3-keto-19-nor steroids (**7**) by standard acid hydrolysis. In addition, treatment of the $\Delta^{5(10)}$ compound (**6**, R = Et) with bromine in pyridine yielded the 4,9-dienone **8**; no reaction of the cyclopropyl ether group with bromine was seen in contrast to earlier bromination studies done in carbon tetrachloride (see above).



The cyclopropyl alcohol **4f** (R = H) in this series was best prepared from its acetate **4f** (R = Ac) by treatment with methyllithium.[20] Potassium bicarbonate treatment of the cyclopropyl acetate yielded mixtures of the desired alcohol and the relatively insoluble *D*-homo ketone **4g**.[11] Attempts at purification gave additional amounts of *D*-homo ketone. The lability of the cyclopropyl alcohol **4f** (R = H) was also demonstrated by its ready conversion to the *D*-homo ketone in spectral grade chloroform. The instability of the 17-acetoxycyclopropane grouping in **4f** (R = Ac) to lithium–ammonia reduction was circumvented by use of the corresponding trimethylsilyl ether of the 17-alcohol **4f** (R = $SiMe_3$), prepared by treatment of the alcohol with hexamethyldisilazane and trimethylchlorosilane. Birch reduction of this ether followed by acid hydrolysis gave the nonconjugated unsaturated ketone **6** (R = H). Further acid treatment followed by acetylation gave the conjugated ketone **7** (R = Ac).

Experimental Section[21]

3β-Acetoxy-17-bromo-*D*-homoandrost-16-en-17a-one (1h, R′ = Ac; X = Br). Ketal Pyrolysis. Procedure A.—A solution of 70 g of 17,17-diethoxyandrostan-3β-ol acetate **1b** (R = Et; R′ = Ac)[22] in 300 ml of cymene was distilled to half-volume over a 5-hr period. The remainder of the solvent was then distilled *in vacuo*. The product, dissolved in 50 ml of pentane containing 1 ml of pyridine, crystallized slowly, yielding 26 g of the enol ether **1c** (R = Et; R′ = Ac): mp 93–95°; 5.80 μ; 52 (18,19-CH_3's), 256 Hz (m, 16-H).

Reaction of Dibromocarbene with the Enol Ether 1c (R = Et; R′ = Ac).—Potassium *tert*-butoxide (10 g) was added to a stirred solution of 24 g of the enol ether **1c** (R = Et; R′ = Ac) in 100 ml of benzene and 30 ml of *tert*-butyl alcohol at −5°.[3] Bromoform (8 ml) in 30 ml of benzene was then added dropwise over a 50-min period (T <5°). After an additional 10 min the solution was poured into water containing a slight excess of acetic acid. The product was isolated by benzene extraction[23] and then acetylated in pyridine–acetic anhydride (95°, 20 min). The acetate, isolated by benzene extraction, was purified by chromatography.[24] The bulk of the product was isoandrosterone acetate (12 g). Fractions (3.1 g) eluted with 1% ethyl acetate–benzene were recrystallized from methylene chloride–hexane to yield 2.2 g of the bromide **1h** (R′ = Ac): mp 227–230° dec; 5.78, 5.90 μ; 257 mμ (ε 5500); 49 (19-CH_3), 63 (18-CH_3), 121 (OAc), 438 Hz (m, 16-H).

Anal. Calcd for $C_{22}H_{31}BrO_3$: C, 62.42; H, 7.38. Found: C, 62.50; H, 7.39.

Bromination of the Cyclopropyl Ether 1f (R = Me; R′ = Ac). Procedure B.—To a well-stirred slurry of 5 g of anhydrous potassium carbonate in 30 ml of carbon tetrachloride containing 0.40 g of the methyl ether **1f** (R = Me; R′ = Ac) at 5° was added 2.2 mol equiv of bromine in carbon tetrachloride solution (0.17 *M*) over a 25-min period. The uptake of bromine was very fast. The mixture was diluted with ice water and extracted with ether (T <10°), yielding an unstable product which was dissolved in dimethylformamide. After 3 days the solution was diluted with water and the product isolated by benzene extraction. The semicrystalline residue was recrystallized from methylene chloride–methanol to yield 155 mg of the bromo ketone **1h** (R′ = Ac), mp 212–213°, identical spectrally with the compound prepared above.

Bromination of the Unsaturated Ketone 1e (R′ = Ac).—The unsaturated ketone **1e** (R′ = Ac; 0.20 g) in 8 ml of carbon tetrachloride was treated with 1.05 mol equiv of bromine (procedure B). After 5 min excess aqueous sodium bisulfite was added and the solution was extracted with methylene chloride. The crude bromine, 130 mg of lithium carbonate, and 5 mg of lithium chloride in 2 ml of dimethylformamide was allowed to stand at room temperature for 65 hr. The solution was diluted with water and the product isolated by methylene chloride extraction. The crystalline residue was recrystallized from methylene chloride–hexane to give 0.18 g of the bromo ketone **1h** (R′ = Ac), mp 213–214°, identical with the above sample.

3β-Hydroxy-17-bromo-*D*-homoandrost-16-en-17a-one (1h, R′ = H; X = Br). Procedure C.—*p*-Toluenesulfonic acid (0.20 g) was added to a boiling solution of the bromide **1h** (R′ = Ac) in 60 ml of methanol and 5 ml of water. After 16 hr half of the methanol was distilled and the solution was diluted with water. The resulting precipitate was collected on a filter, washed with water, and recrystallized from methylene chloride–hexane to yield 0.27 g of **1h** (R′ = H; X = Br): mp 222–224°; 2.73, 5.90 μ; 252 mμ (ε 5350); 48 (19-CH_3), 63 (18-CH_3), 437 Hz (m, 16-H).

Anal. Calcd for $C_{20}H_{29}BrO_2$: C, 67.99; H, 7.67. Found: C, 68.07; H, 7.85.

Attempted saponification of the 3-acetate group of **1h** led to loss of bromine.

3β-Hydroxy-*D*-homoandrostan-17a-one (1g, R′ = H).—A solution of 0.10 g of the bromide **1h** (R′ = H) in 20 ml of ethanol was hydrogenated[25] at atmospheric pressure in the presence of 100 mg of 5% palladium–charcoal catalyst. Although the first 1 mol equiv of hydrogen was taken up rapidly, the second required 3 hr. After removing the catalyst by filtration the solution was diluted with 5 ml of pyridine, concentrated to half-volume, and

(19) A recent patent (German Patent 1,240,078) records the preparation of the methyl ether **5f** (R = Me) and the acetate **5f** (R = Ac) by a similar route.

(20) C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964).

(21) We wish to thank Dr. J. W. Ahlberg and staff for the analyses and spectra reported. The infrared spectra (μ) were determined in chloroform, ultraviolet spectra (mμ) in methanol, and rotations in chloroform (1%). Nmr spectra (hertz) were determined in deuteriochloroform on a Model A-60 spectrometer, Varian Associates, Inc., using tetramethylsilane as an internal standard ($\Delta\nu$ = 0). The mass spectra were determined on a Varian M-66 spectrometer; the relative intensities are recorded in parentheses after each mass peak.

(22) L. Caglioti, G. Cainelli, G. Maina, and A. Selva, *Gazz. Chim. Ital.*, **92**, 309 (1962).

(23) The isolation procedure used throughout this work involved dilution of the reaction mixture with water, extraction with an immiscible solvent, and washing with water and (if acidic) with aqueous bicarbonate solution. The extract was routinely dried over magnesium sulfate and the solvent removed under reduced pressure (T <50°).

(24) The chromatographies described in this section were uniformly run on a weight of Davison silica gel 60 times the weight of the compound involved. We thank Mr. R. T. Nicholson and staff for the competent execution of this work.

(25) We wish to thank Mr. W. M. Selby and staff for the hydrogenations described here.

diluted with water. The resulting precipitate was collected on a filter, washed with water, and recrystallized from aqueous ethanol to yield 60 mg of the alcohol 1g (R′ = H): mp 202–203°; 2.72, 5.82 μ; 48 (19-CH_3), 65 Hz (18-CH_3).

The comparison sample was made by hydrogenation of the Δ^5 derivative of 1g (R′ = H) over palladium–charcoal catalyst in ethanol solution. The reduction required 1.3 hr and yielded a product identical with that obtained above. (An earlier hydrogenation, run at 60 psi, caused overreduction, producing the corresponding 3,17-diol.)

3β-Acetoxy-17-chloro-*D*-homoandrost-16-en-17a-one (1h, R′ = Ac; X = Cl).—Sodium methoxide (3 g) was added to a stirred solution of 4 g of the ethyl ether 1c (R = Et; R′ = Ac) in 100 ml of ether at 5° followed by the rapid addition of 3 ml of ethyl trichloroacetate. After 3.5 hr the mixture was filtered through Super-Cel, water was added, and the product was extracted with ether. The semicrystalline residue was triturated with 1:1 ether–hexane to yield 1.8 g of the crude chloride 1h (R′ = Ac), mp 228–230°. Recrystallization from methylene chloride–hexane afforded the pure sample: mp 239–242°; 5.76, 5.89 μ; 243 mμ (ε 6800); 49 (19-CH_3), 63 (18-CH_3), 420 Hz (q, 16-H).

Anal. Calcd for $C_{22}H_{31}ClO_3$: C, 69.73; H, 8.24; Cl, 9.36. Found: C, 69.53; H, 8.06; Cl, 9.54.

Analysis of the crude reaction product showed 12.5% chlorine (calcd for $C_{24}H_{36}Cl_2O_3$, 15.8), but attempts to isolate a dichloro compound were unsuccessful. Longer treatment with sodium methoxide led to crude products exhibiting a methoxyl signal (226 Hz) in the nmr.

An alternate synthesis of the chloride 1h (R′ = Ac) involved heating a solution of 3 g of the ethyl ether 1c (R′ = Ac) and 20 mg of tetraethylammonium bromide in 5 ml of ethylene oxide and 10 ml of chloroform at 150° for 5 hr.[5] The solution was cooled, washed with water, dried, and concentrated yielding an oil which showed the spectral characteristics of impure unsaturated chloro ketone 1h ($E_{244\ m\mu}$ 3460; found, 10.12% Cl). Again no dichloro derivative was isolable.

Direct addition of the dichloro adduct 1d (R′ = Ac; X = Cl), as produced by the trichloroacetate reaction, to a solution of lithium metal in ammonia containing *tert*-butyl alcohol gave a product which was analyzed by successive chromatography, hydrolysis with aqueous acid, and rechromatography. It was seen to consist of minor amounts of the desired ethyl ether 1f (R′ = H) contaminated with larger amounts of isoandrosterone and *D*-homoisoandrosterone (1g, R′ = H).

3β-Hydroxy-17-chloro-*D*-homoandrost-16-en-17a-one (1h, R′ = H; X = Cl) was prepared from its 3-acetate 1h (R′ = Ac; X = Cl; procedure C) and was recrystallized from methylene chloride–hexane to yield the pure chloride 1h (R′ = H): mp 223–226°; 2.75, 5.87 μ; 244 mμ (ε 3740); 48 (19-CH_3), 63 (18-CH_3), 423 Hz (m, 16-H).

Anal. Calcd for $C_{20}H_{29}ClO_2$: C, 71.30; H, 8.68. Found: C, 70.98; H, 8.65.

Base treatment of the acetate 1h (R′ = Ac) led to loss of halogen.

17,17-Dimethoxyandrostan-3β-ol Acetate (1b, R′ = Ac; R = Me).—Five drops of concentrated sulfuric acid was added to a solution of 52 g of epiandrosterone acetate 1a in 500 ml of methanol and 50 ml of redistilled trimethyl orthoformate. The solution was heated at reflux for 10 min, 15 ml of pyridine was added, and the reaction was cooled. The resulting precipitate was collected on a filter, yielding 50 g of the methyl ketal 1b (R′ = Ac). Recrystallization of a portion from methylene chloride–methanol containing a trace of pyridine gave the pure product: mp 156–159°; 5.75 μ; 49 (18-CH_3), 52 (19-CH_3), 192.5, and 193.0 Hz (OCH_3).

Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.97; H, 10.12. Found: C, 73.14; H, 10.36.

17β-Methoxy-16α,17-cyclopropanoandrostan-3β-ol Acetate (1f, R′ = Ac; R = Me). A. Pyrolysis.—The methyl ketal 1b (45 g, R′ = Ac) was boiled in refluxing cymene for 64 hr (procedure A). The product failed to crystallize but exhibited the proper spectral characteristics for the methyl ether 1c (R′ = Ac): 5.78 μ; 52 (18,19-CH_3's), 213 (OCH_3), 260 Hz (m, 16-H).

B. Methenylation. Procedure D.—Neat diethylzinc (12 ml) was added to a solution of the crude enol ether (32 g) in 230 ml of redistilled *n*-butyl ether, the whole procedure being carried out in a drybox under a slight positive pressure of nitrogen. As methylene iodide (20 ml) was added to the stirred solution dropwise over a 2-hr period, the temperature of the solution rose to 45°. After the reaction was stirred for an additional 16 hr, 50 ml of 2B ethanol was added followed by water and a slight excess of cold dilute hydrochloric acid. The product was extracted with ether. After removal of the solvent, the product crystallized and was recrystallized from methylene chloride–methanol to yield the pure adduct 1f (R = Me; R′ = Ac): 13.8 g; mp 129–130°; 5.80 μ; 38, 41, and 48 (m, cyclopropyl proton signals), 51 (19-CH_3), 60 (18-CH_3), 200 Hz (OCH_3).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.55; H, 9.97.

Chromatography of the mother liquors gave an additional 6.2 g of the same adduct eluted with 2% ethyl acetate–benzene. Elution with 30% ethyl acetate–benzene gave 4.2 g of crude material recrystallized from acetone–hexane to yield 2.3 g of the pure 3-ol 1f (R = Me; R′ = H), mp 192–194°, identical spectrally with the sample prepared below.

17β-Methoxy-16α,17-cyclopropanoandrostan-3β-ol (1f, R′ = H; R = Me). Procedure E.—A slurry of the methyl ether 1f (R′ = Ac, 12 g) in 0.6 l. of methanol and 100 ml of 10% aqueous potassium hydroxide was stirred at room temperature. The steroid dissolved within 15 min, followed by precipitation of the product. After 45 min the mixture was filtered and the precipitate was washed with water, yielding 10.6 g of the product: mp 195–196°; 2.76 μ; 49 (19-CH_3), 59 (18-CH_3), 198 Hz (OCH_3). Recrystallization of a portion of the product from methylene chloride–cyclohexane did not improve the melting point. The cyclopropyl signals in the nmr were similar to those seen in the spectrum of the parent acetate.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.30; H, 10.71.

This derivative was stable in boiling aqueous tetrahydrofuran containing *p*-toluenesulfonic acid. However, in boiling acetic acid containing *p*-toluenesulfonic acid, the known *D*-homo ketone 1g (R′ = Ac) was formed in 60% yield; the remainder of the product was a mixture of the epimeric 16-methylandrostanes (vpc analysis).

17β-Methoxy-16α,17-cyclopropanoandrostan-3-one (2f, R = Me).—The methyl ether 1f (R′ = H, 7.0 g) in 70 ml of pyridine was added to the Sarett reagent[26] prepared from 7 g of chromium trioxide. After 5 hr at room temperature the mixture was diluted with water and extracted with ether. The product was recrystallized from methylene chloride–methanol to yield 4.5 g of the pure ketone 2f (R = Me): mp 149–150°; 5.83 μ; 62 (18,19-CH_3's), 200 Hz (OCH_3). The complex cyclopropyl hydrogen pattern was seen in the nmr at 35–55 Hz.

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.68; H, 10.21.

17β-Methoxy-16α,17-cyclopropanoandrost-2-en-3-ol Acetate (2f, Enol Acetate; R = Me). Procedure F.—A solution of 4.10 g of the ketone 2f (R = Me) and 1.0 g of *p*-toluenesulfonic acid in 50 ml of benzene and 50 ml of isopropenyl acetate was stirred at room temperature for 2 weeks. The product was extracted with ether and crystallized from aqueous methanol to give 3.9 g of the enol acetate. Further recrystallization from methanol gave 0.88 g of the pure material: mp 113–114°; 5.73 μ; 52 (19-CH_3), 62 (18-CH_3), 126 (OAc), 316 Hz (C_6H).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.91; H, 10.02.

A good yield of the 3-ketone (2f, R = Me) was produced by mild alkaline hydrolysis of this enol acetate.

The enol acetate was treated with 1.05 mol equiv of bromine (procedure B). The crude product displayed nmr signals for the enol acetate (126, 316 Hz) but lacked the methoxyl signal; the ir showed a 5.95-μ band, characteristic of an unsaturated ketone.

17β-Ethoxy-16α,17-cyclopropanoandrostan-3β-ol Acetate (1f, R = Et; R′ = Ac).—The ethyl ether 1c (R′ = Ac, 10.8 g) was methylenated (procedure D). The resulting crude product was recrystallized from methylene chloride–methanol to yield 7.8 g of pure adduct: mp 147–149°; 5.78 μ; 51 (19-CH_3), 61 (18-CH_3), 122 Hz (OAc).

Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23; OEt, 12.03. Found: C, 77.25; H, 10.30; OEt, 12.02.

Chromatography of the mother liquors afforded additional acetate 1b (R = Et; R′ = Ac) as well as its 3-hydroxy derivative (see below).

17β-Ethoxy-16α,17-cyclopropanoandrostan-3β-ol (1f, R = Et; R′ = H).—The acetate 1f (R = Et, 5.6 g) was saponified (proce-

(26) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

dure E) yielding 5.2 g of the corresponding alcohol. Recrystallization from acetone–hexane gave the pure material: mp 187–189°; 2.73 μ; 49 (19-CH_3), 59 Hz (18-CH_3). The nmr showed no clear cyclopropyl signals; $[\alpha]D$ +20°; mass spectrum (70 eV) *m/e* 332 (3), 315 (2), 298 (2).

Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92. Found: C, 79.76; H, 10.32.

Treatment of this alcohol with aqueous *p*-toluenesulfonic acid in methanol effected no reaction. At room temperature hydrobromic acid in acetic acid produced the *D*-homo ketone (60%) and a mixture of 16α- (20%) and 16β- (10%) methylandrostanes (by vpc analysis).

17β-Ethoxy-16α,17-cyclopropanoandrostan-3-one (2f, R = Et).—The alcohol 1f (R = Et; R′ = H; 2.8 g) in 30 ml of pyridine was treated with the Sarett reagent[26] from 3 g of CrO_3. After 5 hr the product was isolated by ether extraction and yielded, by recrystallization of the crude product from acetone–hexane, 1.43 g of the ketone 2f (R = Et): mp 142–145°; 5.82 μ; 37, 42, 48, 51 (weak cyclopropyl bands), 62 Hz (18,19-CH_3's); $[\alpha]D$ +51°.

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 82.07; H, 10.38.

Oxidation of this ketone with selenium dioxide or with dichlorodicyanoquinone gave intractable mixtures.

17β-Ethoxy-16α,17-cyclopropanoandrost-2-en-3-ol acetate (3-enol acetate of 2f, R = Et) was prepared from 0.2 g of the ketone 2f (R = Et) by use of procedure F. The product was crystallized from methylene chloride–methanol to yield 0.16 g of the enol acetate: mp 139–140°; 5.72 μ; 51 (19-CH_3), 61 (18-CH_3), 126 (OAc), 316 Hz (C_6H, m).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.48; H, 9.78.

3β,17β-Diacetoxy-16α,17-cyclopropanoandrostane (1f, R = Ac; R′ = Ac).—The enol acetate of isoandrosterone acetate[27] (29 g) was methylenated (procedure D). The crude extract deposited 9 g of crystals from ether which was recrystallized from acetone to yield the pure sample: mp 184–185°; 5.80 μ; 50 (19-CH_3), 55 (18-CH_3), 122 Hz (OAc); mass spectrum (70 eV) *m/e* 388 (1), 373 (10), 346 (100), 328 (40), 217 (40).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.24; H, 9.04.

Chromatography of the mother liquors yielded first the enol acetate 1c (R, R′ = Ac). An additional 7.6 g of adduct 1f (R, R′ = Ac) was obtained by elution with 5% ethyl acetate–benzene followed closely by 7.8 g of isoandrosterone acetate. In addition, 0.45 g of the 3-hydroxy 17-acetate 1f (see below) was eluted at 30% ethyl acetate–benzene. The 3,17-diacetate was stable to iodine in carbon tetrachloride at room temperature for 20 hr.

16α,17-Cyclopropanoandrostane-3β,17β-diol (1f, R, R′ = H).—A mixture of 2 g of the diacetate 1f (R, R′ = Ac) in 200 ml of methanol and 20 ml of 10% aqueous potassium hydroxide was stirred at room temperature for 1.5 hr. The mixture was diluted with water and filtered yielding 1.6 g of product. Recrystallization of a portion of this material from aqueous methanol gave the diol, mp 166–168°, as a hemihydrate: 2.95 μ (KBr); 50 (19-CH_3), 58 Hz (18-CH_3).

Anal. Calcd for $C_{20}H_{32}O_2 \cdot {}^1/_2H_2O$: C, 76.63; H, 10.61. Found: C, 76.65; H, 10.56.

The material was unstable to chromatography on alumina or silica. An alternate preparation of the diol was achieved in good yield by treatment of an ether solution of the diacetate with lithium aluminum hydride at room temperature overnight. Acetylation of the diol with acetic anhydride–pyridine at room temperature afforded the starting diacetate 1f (R, R′ = Ac).

17β-Acetoxy-16,17-cyclopropanoandrostan-3β-ol (1f, R = Ac; R′ = H).—The diacetate 1f (R, R′ = Ac) (1 g) in 70 ml of tetrahydrofuran was diluted with 140 ml of methanol and then with 60 ml of 1:1 water–saturated aqueous potassium bicarbonate solution. The mixture was stirred for 3 hr and was then diluted with water. The resulting precipitate was collected and chromatographed. Early fractions (eluted with 2% ethyl acetate–benzene) yielded 440 mg of crude starting material. Elution with 5% ethyl acetate–benzene gave 390 mg of the crude 17-monoacetate 1f (R = Ac; R′ = H). Recrystallization from methylene chloride–hexane afforded the pure compound: mp 134–136°; 2.76, 5.74 μ; 50 (19-CH_3), 56 (18-CH_3), 122 Hz (OAc).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.49; H, 9.78.

Later fractions contained the D-homo ketone (ir, nmr analysis).

17β-Acetoxy-16,17-cyclopropanoandrostan-3-one (2f, R = Ac). Procedure G.—Jones reagent[28] (1.3 mol equiv of a 4 *N* chromic acid solution) was added dropwise over 2 min to a solution of 0.16 g of the alcohol 1f (R = Ac; R′ = H) in 2 ml of acetone at 5°. After 15 min, excess 2-propanol was added and the reaction mixture was diluted with water. The resulting precipitate was separated and recrystallized from aqueous methanol to yield 60 mg of the ketone 2f (R = Ac): mp 165–166°; 5.70, 5.76 μ; 57 (18-CH_3), 62 (19-CH_3), 121 Hz (OAc); mass spectrum (70 eV) *m/e* 344 (0.03), 329 (10), 312 (100), 287 (100), 284 (100), 233 (100).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.39; H, 9.43.

17β-Hydroxy-16,17-cyclopropanoandrostan-3-one (2f, R = H).—A slurry of the acetate 2f (R = Ac, 0.25 g) in 5 ml of methanol containing 0.25 ml of 10% aqueous potassium hydroxide was stirred at room temperature for 3 hr. (The starting material dissolved after 1 hr.) The solution was diluted with water and the resulting precipitate was collected and recrystallized from aqueous acetone to yield 0.15 g of the hydroxy ketone 2f (R = H): mp 131–134° (resolidifies, remelts at 174–204°); 2.82, 5.82 μ (KBr); 61 (18-CH_3), 63 Hz (19-CH_3).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.49; H, 10.05.

Isomerization of the 3,17-Diol 1f (R, R′ = H). A. Base Catalysis.—A solution of 0.10 g of the diol 1f (R, R′ = H) in 5 ml of methanol containing 0.1 ml of 10% aqueous potassium hydroxide was boiled for 2 hr and then diluted with water. The resulting precipitate was collected and recrystallized from aqueous methanol to yield 76 mg of the *D*-homo ketone 1g (R′ = H), mp 193–195°, identical spectrally with the known compound. The mother liquors contained a mixture of 1g and the 16-methyl androstanes (vpc analysis).

B. Acid Catalysis.—A solution of 100 mg of the diol 1f in 15 ml of acetone and 0.5 ml of water containing 30 mg of *p*-toluenesulfonic acid was boiled for 18 hr. (A similar treatment at room temperature effected no change.) The cooled solution was diluted with water and the resulting precipitate collected. The major component was readily identified as the *D*-homo ketone 1g (R′ = H) by ir, nmr, and vpc. When methanol was used as solvent, after 2.5 hr at reflux, the reaction was half complete; the product contained 3β-hydroxy-16α-methylandrostan-17-one (28%) and the *D*-homo ketone 1g (R′ = H; 18%) by vpc analysis. With a longer reaction time, the epimeric 16β-methylandrostane was formed.

Oxidation of 16α,17-Cyclopropanoandrostane-3β,17β-diol (1f, R, R′ = H). A. Ferric Chloride Oxidation.—A solution of 24 ml of 10% aqueous ferric chloride was added with stirring to a solution of 0.80 g of the diol 1f (R, R′ = H) under a nitrogen atmosphere at 5°. After 20 min, the solution was diluted with water and the resulting precipitate was separated and washed with water. The material was dried and then purified by a short (five fraction) chromatogram, yielding 0.54 g of the pure unsaturated ketone 1e (R′ = H), as indicated by ir, nmr, and uv analysis.

The yield of the 16,17a-diketone 1i (R′ = H; Z = O) from these reactions varied from 2 to 15% and was most readily detected by its characteristic uv absorption (see below).

B. Chromic Acid Oxidation.—Jones reagent[28] (3 ml) was added dropwise to 1 g of the diol 1f (R, R′ = H) in 50 ml of acetone at 5°. After 1.5 hr the solution was diluted with water. The resulting precipitate was dissolved in ether and stirred with 2% aqueous potassium hydroxide. The ether soluble portion yielded a crystalline residue which was recrystallized from methylene chloride–hexane to yield 0.18 g of the pure unsaturated ketone 2e: mp 192–194°; 5.83, 5.96 μ; 223 mμ (ε 7550); 63 (18,19-CH_3's), 350 and 360 (16-H), 402–422 Hz (16,17-H's).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.22; H, 9.41.

The aqueous basic extract was acidified and the resulting precipitate was collected, yielding 0.12 g of the triketone 2i (Z = O), identical with the material produced below.

(27) J. Fajkoš and F. Šorm, *Collect. Czech. Chem. Commun.*, **24**, 766 (1959).

(28) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

3β-Acetoxy-*D*-homoandrost-16-en-17a-one (1e, R′ = Ac).—The methyl ether 1f (R = Me; R′ = Ac) (1 g) and 0.76 g of iodine were mixed in 50 ml of carbon tetrachloride resulting in the slow formation of a heavy purple oil. After 20 hr methylene chloride and excess aqueous sodium thiosulfate were added and the mixture was stirred for 3 hr at room temperature. The product was then isolated by methylene chloride extraction yielding an oil (found, 4.69% I). The product was stirred in 10 ml of dimethylformamide with 0.5 g of lithium carbonate and 0.01 g of lithium chloride. The material, extracted with benzene, was crystallized from methylene chloride–hexane to yield 0.43 g of the unsaturated ketone: mp 148–151°; 5.75, 5.93 μ; 222 (ε 7800) mμ; 51 (19-CH_3), 62 (18-CH_3), 123 Hz (OAc).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.31; H, 9.22.

Chromatography of the mother liquors showed the major impurity to be the known saturated ketone 1g (ir, nmr, and vpc analysis). A similar halogenation procedure using bromine in carbon tetrachloride in the presence of anhydrous potassium carbonate was successful in producing the unsaturated ketone 1e but the accompanying bromo derivative 1h made iodine a superior reagent. Use of bromine in pyridine effected no reaction.

3β-Hydroxy-*D*-homoandrost-16-en-17a-one (1e, R′ = H). A. Dehydration. Procedure H.—Phosphorous oxychloride (35 ml) was added to a solution of 35.8 g of the acetate 1m in 350 ml of pyridine. The mixture was stirred at ambient temperature overnight and was then poured into ice water with stirring. The product (preparation C) extracted with chloroform consisted of a 3:2 mixture of Δ^{16} (1k, R′ = Ac) to $\Delta^{17(20)}$ isomers (vpc analysis).

B. Ozonolysis. Procedure I.—A solution of 10 g of the crude olefin 1k, as produced above, in 250 ml of methylene chloride and 3 ml of pyridine was treated with a stream of ozonized oxygen at −70° until a blue color appeared. Zinc dust (15 g) and 60 ml of acetic acid was added and the mixture was stirred for 1 hr in an ice bath. The mixture was filtered and the filtrate extracted with methylene chloride. The product was purified by chromatography. The 17-ketone 1a (R′ = Ac, 3.0 g) was eluted at 10% ethyl acetate–benzene, followed by the amorphous ketoaldehyde 1j (R′ = Ac; Y = H; 3.3 g): 3.68, 5.78, 5.84 μ (sh); 48 (19-CH_3), 65 (18-CH_3), 120 (OAc), 127 Hz ($COCH_3$).

C. Cyclization. Procedure J.—A solution of 2.6 g of the ketoaldehyde 1j (R′ = Ac) in 250 ml of methanol and 50 ml of 10% aqueous potassium hydroxide was boiled under an atmosphere of nitrogen for 1 hr. The methanol solution was diluted with 100 ml of water, the methanol was distilled, and the resulting mixture was extracted with methylene chloride. The product was recrystallized from ether and from acetone–hexane to yield the unsaturated ketone 1e (R′ = H): mp 182–184°; 2.76, 5.97 μ; 222 mμ (ε 8500); 48 (19-CH_3), 61 (18-CH_3), 349 and 361 (m, 16-H), 404–423 Hz (m, 17-H); mass spectrum (70 eV) *m/e* 302 (5), 274 (10), 256 (4).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.10; H, 10.29.

Saponification of the acetate 1e (procedure E) also led to a good yield of the alcohol 1e.

***D*-Homoandrosta-4,16-diene-3,17-dione (2e, Δ^4). A. Ozonolysis.**—A solution of 10 g of 17-methylandrosta-4,16-dien-3-one (2k, Δ^4) was ozonized (procedure I) using a total of 1.2 mol equiv of ozone. The product was chromatographed and yielded 3.1 g of amorphous ketoaldehyde which crystallized poorly on ether trituration as a solvate: 3.66 (w), 5.80, 5.98 μ; 68 (18-CH_3), 72 (19-CH_3), 128 (Ac), 344 Hz (C_6H).

B. Cyclization.—The ketoaldehyde 2j (Y = H; Δ^4) was cyclized (procedure J) and the resulting product was purified by chromatography. The crystalline material (0.44 g) eluted with 5% ethyl acetate–benzene was recrystallized from acetone to give the dienedione as a hemiacetonate: mp 184–187°; 5.98 μ; 235 mμ (ε 20,000); 64 (18-CH_3), 72 (19-CH_3), 355 Hz (m, 15-H); mass spectrum (70 eV) *m/e* 298 (10), 256 (8), 175 (3), 124 (5).

Anal. Calcd for $C_{20}H_{26}O_2 \cdot {}^1/_2C_3H_6O$: C, 78.86; H, 8.93. Found: C, 79.23; H, 9.00.

When the unpurified ketoaldehyde was used in this cyclization an acidic portion was isolated by extraction. This material was recrystallized from acetone–hexane to yield **3,17-diketo-17-methyl-16,17-secoandrost-4-en-16-oic acid**: mp 207–210°; 5.83, 5.98 μ; 241 mμ (ε 16,200); 61 (18-CH_3), 72 (19-CH_3), 132 (Ac), 347 Hz (4-H); mass spectrum (70 eV) *m/e* 332 (2), 314 (1), 289 (5), 272 (1), 230 (1).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.17; H, 8.42.

3-Methoxy-*D*-homoestra-1,3,5(10),16-tetraen-17a-one (4e).—3-Methoxy-17α-methylestra-1,3,5(10)-trien-17-ol (4m) was dehydrated and ozonized (procedures H, I). The product was chromatographed and the crude ketoaldehyde 4j (14 g of material eluted with 5% ethyl acetate–benzene) was treated in 150 ml of methanol with 15 ml of 5% aqueous potassium hydroxide at room temperature for 45 min. The product was isolated by benzene extraction and chromatographed. Early fractions (6.8 g) from the column were largely unreacted ketoaldehyde 4j eluted at 2% ethyl acetate–benzene. Elution with 5% ethyl acetate–benzene gave fractions which were recrystallized from acetone–hexane (Darco) to give 1.83 g of **3-methoxy-*D*-homoestra-1,3,5(10)-trien-15β-ol-17a-one** (4i, Z = β-OH, H): mp 177–179°; 2.81, 5.89 μ (KBr); 68 (18-CH_3), 215–240 (15α-H), 226 Hz (OMe). The ultraviolet spectrum showed only the A ring chromophore.

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.60; H, 8.27.

The ketol 4i (Z = OH, 0.75 g) was treated with base (procedure J) and yielded, by dilution of the reaction mixture with water, 0.62 g of the unsaturated ketone 4e. Recrystallization from acetone–hexane gave 0.47 g of the pure material: mp 162–164°; 6.01 μ; 222 mμ (ε 15,700; enhanced uv due to the A ring chromophore); $[\alpha]_D$ −1°.

Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.04; H, 8.07.

The same material was isolated by base treatment of the crude ketoaldehyde 4j (Y = H) followed by chromatography. Hydrogenation of the unsaturated ketone proceeded readily to give in good yield the known saturated ketone 4g.[11]

3β-Acetoxy-17-keto-17-methyl-16,17-secoandrostan-16-oic Acid (1j, R′ = Ac; Y = OH).—Sodium metaperiodate (12.5 g) in 125 ml of water was added to a suspension of 2.2 g of ruthenium dioxide (54%) in 500 ml of acetone.[17] A solution of 11 g of "preparation C" (the crude olefin 1k, R′ = Ac) in 500 ml of acetone was added over a 30-min period. An additional 25 g of sodium metaperiodate in 150 ml of water was then added over a 1-hr period. After a total reaction time of 4 hr, the reaction was diluted with 50 ml of 2-propanol. The black precipitate was filtered and the filtrate was concentrated to 100 ml at T <20°. The remainder was diluted with saturated sodium chloride solution and extracted with ethyl acetate. The extract was washed twice with iced 2% potassium hydroxide solution. The basic washes were acidified and extracted in turn with ethyl acetate. The latter yielded 2.17 g of the crystalline acid which was further purified by recrystallization from ether–hexane to give the pure compound: mp 153–156°; 5.82 μ; 49 (19-CH_3), 64 (18-CH_3), 121 (OAc), 132 Hz (Ac).

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.54; H, 8.92.

3β-Hydroxy-17-keto-17-methyl-16,17-secoandrostan-16-oic acid (1j, R′ = H; Y = OH) was prepared by saponification of the corresponding acetate (procedure E) and was crystallized from methylene chloride–hexane to yield the pure alcohol: mp 179–185°; 2.90, 5.85 μ (KBr); 46 (19-CH_3), 62 (18-CH_3), 130 Hz (Ac).

Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.37; H, 9.56.

3β-Hydroxy-17-keto-17-methyl-16,17-secoandrostan-16-oic Acid Methyl Ester (1j, R′ = H; Y = OMe).—The hydroxy acid 1j (R′ = H; Y = OH; 0.90 g) was suspended in 250 ml of ether. Diazomethane, prepared from 2 g of *N*-nitroso-*N*-methylurea in 100 ml of ether, was added. The mixture was stirred 1 hr. (The starting material dissolved during this time.) The solvent was evaporated and the residue crystallized from methylene chloride–hexane to yield 0.67 g of the ester: mp 143–145°; 2.86, 5.76, 5.88 μ; 48 (19-CH_3), 61 (18-CH_3), 130 (Ac), 217 Hz (OMe).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.10; H, 9.88.

3β-Acetoxy-17-keto-17-methyl-16,17-secoandrostan-16-oic acid methyl ester (1j, R′ = Ac; Y = OMe) was prepared by essentially the same procedure yielding crystalline material which was recrystallized from ether–hexane to give the pure compound: mp 127–129°; 5.76, 5.88 μ; 49 (19-CH_3), 62 (18-CH_3), 122 (OAc), 133 (Ac), 221 Hz (OMe).

Anal. Calcd for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.02; H, 9.51.

3β-Hydroxy-*D*-homoandrostane-16,17a-dione (1i, R′ = H; Z = O).—Sodium methoxide (0.10 g) was added to a solution of 0.45 g of the ester 1j (R′ = H; Y = OMe) in 4 ml of anhydrous benzene. The mixture was stirred under nitrogen for 18 hr and was poured into a mixture of ice water and ether. The aqueous layer was separated and acidified with sodium dihydrogen phosphate. The resulting precipitate was separated and washed with water to give 380 mg of the diketone. Recrystallization from ethyl acetate gave the pure compound: mp 260–263°; 2.80, 2.96, 6.18 μ (KBr); 255 mμ (ε 16,800) [in 0.1 *N* KOH–MeOH, 282 mμ (ε 29,300)].

Anal. Calcd for $C_{20}H_{30}O_3$: C, 73.30; H, 8.95. Found: C, 73.40; H, 9.31.

The 3-acetate 1j (R′ = Ac; Y = OMe) underwent a similar conversion in good yield to provide the same diketone (1i, R′ = H).

***D*-Homoandrostane-3,16,17a-trione (2i, Z = O).**—The 3-hydroxyl derivative 1i (R′ = H; Z = O) was oxidized at 5° for 40 min with 1.7 ml of Jones reagent. The mixture was diluted with water and the resulting precipitate was separated. Recrystallization from aqueous methanol gave the pure sample: mp 292–295° dec; 5.82, 6.20 μ (KBr); in 0.1 *N* KOH–MeOH, 284 mμ (ε 24,700).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.69; H, 9.00.

3β,5α-Diacetoxyandrostan-17-one (3a, R′, R″ = Ac).—Acetic anhydride (2 ml) containing 0.40 g of *p*-toluenesulfonic acid was diluted with 20 ml of acetic acid and 20 ml of acetic anhydride. 3β,5α-Dihydroxyandrostan-17-one[12] (10.0 g) was then added. The mixture was stirred in a water bath at room temperature for 4 hr, was cooled to 5°, and was diluted with ice water. The resulting mixture was stirred at 5° for 1 hr and then filtered, washing the precipitate with water. The product was recrystallized from aqueous acetone to yield 11.4 g of the pure diacetate: mp 155–158°; 5.73 μ; 53 (18-CH_3), 64 (19-CH_3), 121 (OAc), and 123 Hz (OAc).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.72; H, 8.56.

3β,5α-Diacetoxyandrostan-17-one Diethyl Ketal (3b, R = Et; R′, R″ = Ac.) Procedure K.—To a slurry of 11.1 g of the diacetate 3a (R′, R″ = Ac) in 15 ml of 2B ethanol, 15 ml of benzene, and 30 ml of triethyl orthoformate was added 0.4 ml of concentrated sulfuric acid. The mixture was stirred at room temperature for 2 hr and then treated with 2 ml of tetramethyl guanidine. The resulting colorless solution was diluted with water and the product extracted with benzene. Recrystallization of the product from ether–methanol gave 6.4 g of 17β-ethoxy-17-methoxyandrostane-3β,5α-diol diacetate as a hemimethanolate: mp 176–177°; 5.78 μ; 52 (18-CH_3), 61 Hz (19-CH_3).

Anal. Calcd for $C_{27}H_{44}O_6 \cdot {}^1/_2CH_4O$: C, 68.71; H, 9.65. Found: C, 68.62; H, 9.38.

When the crude ketal was triturated with ether, the *diethyl* ketal 1b (R = Et) crystallized (nmr analysis).

Reaction of Ethyl Orthoformate with 3β,5α-Dihydroxyandrostan-17-one (3a, R′, R″ = H).—The dihydroxy ketone 3a (5 g) was treated with ethyl orthoformate (procedure K) yielding an amorphous product: 2.75, 5.80 (m) μ; the nmr showed many methyl group signals as well as a broad signal at 323 Hz for the C-6 vinyl proton and the C-3α proton. The product was then pyrolyzed in cymene (procedure A) and the resulting material chromatographed. **3β-Formyloxyandrost-5-en-17-one** was eluted at 5% ethyl acetate–benzene and recrystallized from ether. It had mp 145–147°; 5.75 μ; 53 (18-CH_3), 64 (19-CH_3), 324 and 328 (C_6H), 483 Hz (HCO_2).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 76.14; H, 8.88.

Elution of the column with 50% ethyl acetate–benzene gave 1.0 g of crude monoformate which recrystallized from acetone–hexane to yield **3β,5α-dihydroxyandrostan-17-one 3-formate**: mp 184–186°; 2.76, 5.76 μ; 52 (18-CH_3), 62 (19-CH_3), 483 Hz (HCO_2); $[\alpha]_D$ +56°.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.90; H, 9.03.

Later eluents afforded 0.2 g of the starting diolone 3a (R′, R″ = H). The monoformate was also prepared by dissolving dehydroisoandrosterone in formic acid; after 1 hr at room temperature, addition of water gave the desired compound. A similar treatment of the diolone 3a (R′, R″ = H) afforded in high yield its monoformate.

17β-Ethoxyandrost-16-ene-3β,5α-diol Diacetate (3c, R = Et; R′, R″ = Ac).—The diethyl ketal 3b (R = Et; R′, R″ = Ac; 67 g) was boiled in cymene (procedure A) and afforded, by direct crystallization from methanol, 26 g of the enol ether, mp 130–135°. Recrystallization from methanol containing a trace of pyridine gave the pure product, mp 136–138°, 2.75 μ.

Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.79; H, 9.28.

17β-Ethoxy-16α,17-cyclopropanoandrostane-3β,5α-diol Diacetate (3f, R = Et; R′, R″ = Ac).—The enol ethyl ether 3c (R′, R″ = Ac) was treated with methylene iodide (procedure D) yielding 18.5 g (72%) of the recrystallized (methylene chloride–methanol) cyclopropyl derivative: mp 194–197°; 5.78 μ; 61 (19-CH_3), 63 Hz (18-CH_3).

Anal. Calcd for $C_{26}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 72.09; H, 9.09.

17β-Ethoxy-16α,17-cyclopropanoandrostane-3β,5α-diol 5-Acetate (3f, R = Et; R′ = H; R″ = Ac).—A slurry of 1.40 g of the diacetate 3f (R = Et) in 150 ml of methanol, 5 ml of water, and 5 ml of saturated aqueous potassium bicarbonate was stirred at room temperature for 8 hr. The solution was diluted with water and the product collected by filtration. The water-washed and air-dried precipitate was recrystallized from acetone–hexane to yield 1.05 g of the pure 3-hydroxy derivative: mp 203–205°; 2.75, 5.78 μ; 62 (18,19-CH_3's), 122 Hz (OAc); $[\alpha]_D$ +35°.

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.75; H, 9.99.

The same material was produced by boiling the diacetate in methanol containing aqueous potassium hydroxide for 2 hr.

17β-Ethoxy-16α,17-cyclopropanoandrostane-3β,5α-diol (3f, R = Et; R′, R″ = H). Procedure L.—A solution of 3.0 g of the diacetate 3f (R = Et) in 200 ml of ether was added to a stirred slurry of 1.8 g of lithium aluminum hydride in 300 ml of ether over a 10-min period. After an additional 4 hr of stirring at room temperature, the solution was diluted cautiously and consecutively with 140 ml of ethyl acetate, 7 ml of water, and 2 ml of 10% aqueous potassium hydroxide. The resulting mixture was filtered through a mixture of magnesium sulfate and Super-Cel. The crystalline product, obtained by concentration of the filtrate, was recrystallized from acetone to give 1.8 g of the diol: mp 215–217°; 2.88 μ (KBr); 55 Hz (18,19-CH_3's) (DMSO-d_6); $[\alpha]_D$ +26°.

Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.43; H, 10.60.

17β-Ethoxy-5α-acetoxy-16α,17-cyclopropanoandrostan-3-one (2f, R = Et; 5α-OAc).—A solution of 0.85 g of the 3-alcohol 3f (R = Et; R″ = Ac) in 12 ml of pyridine was treated with the Sarett reagent[26] from 2.0 g of chromic acid at 5° for 10 min and at room temperature for 6 hr. The mixture was then diluted with water and the product isolated by ether extraction. Recrystallization of the material obtained from acetone gave 0.60 g of the ketone: mp 184–187°; 5.75, 5.82 μ (sh); 63 (18-CH_3), 73 Hz (19-CH_3).

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.82; H, 9.12.

17β-Ethoxy-16α,17-cyclopropanoandrost-4-en-3-one (2f, R = Et; Δ^4).—A solution of 0.34 g of the 3-ketone 2f (R = Et; 5α-OAc) in 50 ml of methanol, 5 ml of water, and 5 ml of saturated aqueous potassium bicarbonate was heated at reflux under an atmosphere of nitrogen for 16 hr. The solution was diluted with water and the methanol was distilled. The resulting precipitate was collected on a filter, washed with water, dried, and recrystallized from acetone–hexane to yield the unsaturated ketone: mp 166–168°; 5.98 μ; 241 mμ (ε 15,900); 63 (18-CH_3), 72 (19-CH_3), 343 Hz (4-H); $[\alpha]_D$ +125°.

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.60; H, 9.66.

Androst-16-ene-3β,5α,17-triol Triacetate (3c, R, R′, R″ = Ac).—A solution of the dihydroxy ketone 3a (6.5 g) in 200 ml of isopropenyl acetate containing 0.4 g of *p*-toluenesulfonic acid was distilled to half volume over an 18-hr period. The product, extracted from the cooled solution with ether, was dissolved in 1 l. of hexane and passed over a short chromatographic column containing 200 g of Florisil. The adsorbent was washed with 4 l. of 80% benzene–hexane, the solvent distilled, and the resulting crystalline material recrystallized from methanol to yield 4.4 g of the enol acetate: mp 152–153°; 5.75 μ; 53 (18-CH_3), 63 (19-CH_3), 118, 123, 128 (OAc's), 324–328 Hz (16-H).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.24; H, 8.50.

16α,17-Cyclopropanoandrostane-3β,5α,17β-triol Triacetate (3f, R, R′, R″ = Ac).—The enol acetate (3c, R, R′, R″ = Ac; 4.3 g) was methylenated (procedure D) to afford, by recrystallization from methylene chloride–methanol, 2.50 g of the adduct: mp 230–233°; 5.75 μ; 56 (18-CH_3), 62 (19-CH_3), 120 (OAc), 124 Hz (OAc); $[\alpha]_D$ +31°.

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.76; H, 8.51.

Chromatography of the mother liquors afforded an additional adduct as well as smaller amounts of the starting enol acetate 3c and the 17-ketone 3a. The triacetate was also prepared by acetylation of the 5-monoacetate 3f (R, R′ = H; R″ = Ac) with pyridine–acetic anhydride at room temperature.

16α,17-Cyclopropanoandrostane-3β,5α,17-triol (3f, R, R′, R″ = H).—The triacetate 3f (0.28 g) was reduced with $LiAlH_4$ (procedure L) and yielded a crystalline residue which was recrystallized from acetone–ethyl acetate to give the triol (as a solvate with 1 mol equiv of ethyl acetate): mp 178–182°; 2.88, 5.73 μ (EtOAc); 52 (18-CH_3), 54 Hz (19-CH_3) (DMSO-d_6).

Anal. Calcd for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.60; H, 9.82.

3β,5α-Dihydroxy-*D*-homoandrostan-17a-one 5-Acetate (3g, R′ = H; R″ = Ac).—The triacetate (1 g) was treated with base (procedure E) yielding 0.75 g of crystals which were recrystallized from aqueous methanol to give the pure material: mp 207–210°; 2.75, 2.79, 5.84 μ; 60 (19-CH_3), 66 (18-CH_3), 122 Hz (OAc).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.68; H, 9.26.

A similar treatment of the diol 3f (R, R′ = H; R″ = Ac) with base gave the same D-homo ketone (3g, R′ = H; R″ = Ac).

3β,5α-Diacetoxy-*D*-homoandrostan-17a-one (3g, R′, R″ = Ac) was prepared from the monoacetate 3g (R′ = H; R″ = Ac) with pyridine–acetic anhydride at 95°. The product was recrystallized from acetone–hexane to yield the diacetate: mp 142–143°; 5.75, 5.83 μ; 61 (19-CH_3), 66 (18-CH_3), 120 (OAc), 124 Hz (OAc).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.61; H, 8.51. Found: C, 71.85; H, 8.91.

5α-Acetoxy-*D*-homoandrostane-3,17a-dione (2g, 5α-OAc).—The alcohol 3g (R′ = H; R″ = Ac) was oxidized with Jones reagent[28] (procedure G) and furnished, by dilution of the reaction mixture with water, 0.54 g of the diketone (2g, 5α-OAc). Recrystallization from aqueous acetone gave the pure material: mp 180–181°; 5.78 μ; 67 (18-CH_3), 72 (19-CH_3), 118 Hz (OAc).

Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.40; H, 9.14.

Treatment of this compound in aqueous methanol with potassium bicarbonate afforded in good yield the known unsaturated diketone (2g, Δ^4).

16α,17-Cyclopropanoandrostane-3β,5α,17-triol 5-Acetate (3f, R, R′ = H; R″ = Ac).—Saturated potassium bicarbonate solution (10 ml) and 10 ml of water were added to a solution of 1 g of the triacetate 3f (R, R′, R″ = Ac) in 150 ml of methanol. The mixture was stirred at room temperature for 7.5 hr and the methanol was then evaporated in a stream of nitrogen (T <35°). The mixture was diluted with water and the resulting precipitate was separated, dried, and recrystallized twice from acetone–cyclohexane to afford 0.51 g of the diol as a hemiacetonate: mp 173–178°; 2.98, 5.80 μ; 53 (18-CH_3), 58 (19-CH_3), 118 Hz (OAc); $[\alpha]_D$ +29°.

Anal. Calcd for $C_{22}H_{34}O_4 \cdot {}^1/_2C_3H_6O$: C, 72.09; H, 9.53. Found: C, 71.81; H, 9.71.

The mother liquors were chromatographed on acid-washed alumina. Fractions eluted with 20% ethyl acetate–benzene were combined and recrystallized from ether–hexane to yield 0.11 g of **16α,17-cyclopropanoandrostane-3β,5α,17-triol 5,17-diacetate (3f, R, R″ = Ac; R′ = H)**: mp 179–181°; 2.78, 5.79 μ; 53 (18-CH_3), 57 (19-CH_3), 117 and 119 Hz (OAc); $[\alpha]_D$ +29°.

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.19; H, 9.03.

In a similar experiment the mother liquors were chromatographed on alkaline alumina (Merck). The chief product was eluted, after a 2-day interval, with 5% ethyl acetate–benzene and recrystallized from methylene chloride–hexane to yield pure **16α,17-cyclopropanoandrost-5-ene-3β,17-diol 17-acetate (1f, Δ^5; R = Ac; R′ = H)**: mp 118–126°; 2.75, 5.72 μ; 55 (18-CH_3), 62 (19-CH_2), 120 (OAc), 320 Hz (m, C_6 H); mass spectrum (70 eV) m/e 344 (1), 326 (2), 302 (10), 284 (5).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.34; H, 9.61.

5α,17β-Acetoxy-16α,17-cyclopropanoandrostan-3-one (2f, R = Ac; 5α-OAc).—The alcohol 3f (R, R″ = Ac; R′ = H; 6 g) was oxidized with Jones reagent[28] (procedure G) and afforded, after recrystallization of the product from methylene chloride–methanol, 2.87 g of the ketone (as a hemimethanolate): mp 170–177°; 5.75 μ; 57 (18-CH_3), 72 (19-CH_3), 118 (OAc), 120 Hz (OAc).

Anal. Calcd for $C_{24}H_{34}O_5 \cdot {}^1/_2CH_4O$: C, 70.30; H, 8.67. Found: C, 70.68; H, 8.62.

3β,5α-Dihydroxyandrostan-17-one 5-Acetate (3a, R′ = H; R″ = Ac).—A solution of 2 g of the diacetate 3a in 70 ml of methanol containing 5 ml of saturated aqueous potassium bicarbonate and 5 ml of water was heated at reflux for 0.5 hr. Water was added, the methanol was distilled, and the resulting precipitate was collected. Recrystallization of this material from aqueous methanol and then methylene chloride–hexane gave the monoacetate: mp 152–157°; 2.75, 5.75 μ; 52 (18-CH_3), 62 (19-CH_3), 122 Hz (OAc); $[\alpha]_D$ +73°.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.30; H, 9.43.

Dehydroacetoxylation of 3a (R′ = H; R″ = Ac) on Alumina.—A solution of 0.29 g of the monoacetate 3a (R′ = H; R″ = Ac) in benzene was put on 20 g of alumina (Merck). After 5 days elution with 10% ethyl acetate–benzene gave 20 mg of androstenedione. Elution with 30% ethyl acetate–benzene gave 0.26 g of dehydroisoandrosterone contaminated with 10% of the starting 5α-acetate (ir, nmr, tlc analysis).

17β-Acetoxy-16α,17-cyclopropanoandrost-4-en-3-one (2f, R = Ac; Δ^4). A. Oppenauer Oxidation.—A solution of 0.40 g of the alcohol 1f (R = Ac; R′ = H; Δ^5) and 1 ml of redistilled cyclohexanone in 60 ml of toluene was distilled to a volume of 50 ml. Aluminum isopropoxide (0.45 g) in 3 ml of toluene was added to this boiling solution over a 2-min period. After 15 min more the solution was cooled and excess Rochelle salts solution was added. The mixture was steam distilled for 0.5 hr resulting in the precipitation of a crystalline product. Separation of this material followed by recrystallization from methylene chloride–hexane gave the ketone: mp 208–211°; 5.72, 6.01 μ; 239 mμ (ε 16,500); 57 (18-CH_3), 70 (19-CH_3), 121 (OAc), 343 Hz (4 H).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.95; H, 8.47.

The same reagent converted the diacetate 3f (R, R″ = Ac; R′ = H) to 2f (R = Ac; Δ^4) using a 3-hr reflux period.

B. Dehydroacetoxylation.—The ketone 2f (2.6 g, R = Ac; 5α-OAc) was dissolved in 250 ml of benzene and adsorbed on a chromatographic column of 260 g of alumina (Merck). After 1 hr, the steroid was eluted with 20% ethyl acetate–benzene and recrystallized from methylene chloride–hexane to yield 2.0 g of the pure unsaturated ketone 2f (R = Ac; Δ^4), identical with the material prepared above.

17β-Hydroxy-16α,17-cyclopropanoandrost-4-en-3-one (2f, R = H; Δ^4).—The acetate 2f (R = Ac; Δ^4; 0.90 g) was hydrolyzed according to procedure E for 2.5 hr. The product (0.78 g) was recrystallized from aqueous acetone and had mp 101–111°; 2.72, 6.00 μ; 62 (18-CH_3), 73 (19-CH_3), 344 Hz (C_4 H).

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.93; H, 9.52.

3-Methoxy-17β-ethoxy-16α,17-cyclopropanoestra-1,3,5(10)-triene (4f, R = Et).—The diethyl ketal of estrone methyl ether (4b, 65 g), prepared by ketalization of the 17-ketone (procedure K), was boiled in cymene for 46 hr (procedure A). The resulting enol ether (amorphous) was methylenated (procedure D) without purification, yielding, by crystallization from methanol, 32 g of the adduct 4f: mp 88–90°; no carbonyl absorption in the ir; no selective uv absorption beyond that of the aromatic A ring absorption; 62 (18-CH_3), 227 Hz (OMe); $[\alpha]_D$ +84°; mass spectrum (70 eV) m/e 326 (5), 311 (1), 298 (1), 218 (3), 174 (3), 147 (3).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.92; H, 9.45.

The mother liquors consisted mainly of the adduct 4f (R = Et) and *ca.* 20% of the starting 17-ketone as shown by chromatographic analysis.

3-Methoxy-17β-ethoxy-16α,17-cyclopropanoestra-2,5(10)-diene (5, R = Et). Procedure M.—A solution of 23 g of the adduct

4f (R = Et) in 400 ml of tetrahydrofuran was added to 800 ml of ammonia and 400 ml of *tert*-butyl alcohol. Lithium rod (5 g) was added portionwise over a 10-min period. After a total of 40 min, excess solid ammonium chloride was added to decolorize the solution. The ammonia was distilled, water was added, and the solvents were steam distilled. The cooled aqueous mixture crystallized on cooling and the product was collected on a filter. Recrystallization of this material from methylene chloride–methanol gave 19.2 g of the product: mp 93–95°; 5.89 (m), 6.01 μ (m); no selective uv absorption; 61 (18-CH_3), 212 Hz (OCH_3); $[\alpha]D$ +94°; mass spectrum (70 eV) *m/e* 328 (2), 204 (1), 146 (3).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83. Found: C, 80.55; H, 9.71.

17β-Ethoxy-16α,17-cyclopropanoestr-5(10)-en-3-one (6, R = Et). Procedure N.—The reduction product **5** (R = Et; 5.0 g) was stirred in 95% aqueous acetic acid. The crystals dissolved in 15 min. After 25 min, the solution was diluted with water and the resulting precipitate was separated by filtration. Recrystallization of the product from aqueous methanol gave 4.0 g of the unsaturated ketone: mp 94–98°; 5.80 μ; no selective uv absorption; 62 Hz (18-CH_3); $[\alpha]D$ +174°.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.24; H, 9.64.

17β-Ethoxy-16α,17-cyclopropanoestra-4,9-dien-3-one (8).—The unconjugated ketone (3 g) from the preceding experiment in 30 ml of pyridine at 5° was treated with 4.0 g of pyridinium bromide perbromide. After 15 min the mixture was diluted with water and the resulting dibromide was separated by filtration and displayed a band at 5.00 μ. The dibromide was dissolved in 50 ml of pyridine and after 1 hr the solution was diluted with water and extracted with benzene. The semicrystalline residue was recrystallized from ether–hexane (Darco) to yield 2.2 g of the dienone **8**: mp 102–104°; 6.00 μ; 304 mμ (ε 20,700); 72 (18-CH_3), 342 Hz (C_4H); $[\alpha]D$ −160°.

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.95; H, 8.67.

17β-Ethoxy-16α,17-cyclopropanoestr-4-en-3-one (7, R = Et). Procedure O.—A solution of 1.4 g of the dihydroaromatic ether (**5**, R = Et) in 30 ml of methanol, 6 ml of water, and 2.4 ml of concentrated hydrochloric acid was allowed to stand at room temperature for 2 hr. The resulting mixture was diluted with water and filtered. The insoluble material was recrystallized from aqueous acetone to yield 1.25 g of the unsaturated ketone **7** (R = Et): mp 130–133°; 5.99 μ; 239 mμ (ε 11,600); 65 (18-CH_3), 350 Hz (4 H); $[\alpha]D$ +71°.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.91; H, 9.42.

3-Methoxy-17β-acetoxy-16α,17-cyclopropanoestra-1,3,5(10)-triene (4f, R = Ac).—The enol acetate of estrone methyl ether[29] (30 g) was methylenated (procedure D). The product was taken up in 200 ml of methanol containing 20 ml of saturated aqueous potassium bicarbonate and 20 ml of water. After 15 min the solution deposited a crop of crystals. The mixture was diluted with water and filtered. The dried crystals were triturated with ether to remove estrone methyl ether (16 g). A portion (14 g) of the ether soluble material was chromatographed and the crude adduct (3.1 g), eluted at 5% ethyl acetate–benzene, was recrystallized from ether–methanol to yield 1.77 g of the adduct: mp 95–96°; 5.72 μ; 57 (18-CH_3), 122 Hz (OAc); $[\alpha]D$ +54°; mass spectrum (70 eV) *m/e* 340 (10), 298 (10), 228 (3), 213 (2), 186 (2), 173 (3).

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.52; H, 8.26.

3-Methoxy-16α,17-cyclopropanoestra-1,3,5(10)-trien-17-ol (4f, R = H).—A solution of methyllithium in ether (1 *M*, 4.5 ml) was added to a solution of 0.80 g of the acetate **4f** (R = Ac) in 24 ml of ether at 5° over a 10-min period.[20] After an additional 10 min the reaction was poured into a stirred suspension of excess boric acid in 50 ml of water. A semicrystalline product, obtained by ether extraction, was recrystallized from ether–hexane to yield 0.46 g of the pure alcohol **4f** (R = H): mp 115–130°; 2.78 μ (KBr); 60 Hz (18-CH_3); mass spectrum (70 eV) *m/e* 298 (5), 228 (1), 213 (1), 186 (1), 173 (1).

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.61; H, 8.92.

Spectral grade chloroform was sufficiently acidic to cause transformation of the cyclopropyl alcohol **4f** (R = H) to the *D*-homo ketone **4g**, as demonstrated by the ensuing ir spectrum.

In other runs with methyllithium, under less carefully controlled conditions, the *D*-homo ketone **4g** contaminated the product so that crystallization and purification could not be effected. When attempts were made to use potassium hydroxide or potassium bicarbonate (all at room temperature) the chief product obtained was the *D*-homo ketone **4g**. This material was identical spectrally with the known compound.[11]

3-Methoxy-17β-trimethylsilyloxy-16α,17-cyclopropanoestra-1,3,5(10)-triene (4f, R = $SiMe_3$).—Hexamethyldisilazine (15 ml) was added to a stirred solution of 1.5 g of the alcohol **4f** (R = H) in 150 ml of pyridine followed by the addition of 7.5 ml of trimethylsilyl chloride. The reaction mixture was stirred at room temperature for 2 hr and then poured into ice water. The resulting precipitate was separated, washed with water, dried, and recrystallized from hexane to yield the pure silyl ether: mp 112–114°; 58 Hz (18-CH_3).

Anal. Calcd for $C_{23}H_{34}O_2Si$: C, 74.54; H, 9.25. Found: C, 74.87; H, 9.17.

3-Methoxy-17β-trimethylsilyloxy-16α,17-cyclopropanoestra-2,5(10)-diene (5, R = $SiMe_3$).—The silyl ether **4f** (R = $SiMe_3$; 1.5 g) was reduced as in procedure M. The product crystallized from pentane to yield 0.71 g of the reduced compound: mp 111–113°; 58 Hz (18-CH_3).

Anal. Calcd for $C_{23}H_{36}O_2Si$: C, 74.14; H, 9.74. Found: C, 74.06; H, 9.80.

17β-Hydroxy-16α,17-cyclopropanoestr-5(10)-en-3-one (6, R = H).—The dihydroaromatic ether **5** (R = $SiMe_3$) was treated according to procedure N and yielded a crystalline product which was recrystallized from aqueous methanol to yield the product: mp 137–148°; 5.83 μ; 58 Hz (18-CH_3).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.31; H, 9.22.

17β-Acetoxy-16α,17-cyclopropanoestr-5(10)-en-3-one (6, R = Ac) was prepared by acetylation of the corresponding alcohol at room temperature with pyridine–acetic anhydride. The product was recrystallized to give the pure material: mp 137–140°; 5.74, 5.82 μ.

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.52; H, 8.70.

Attempts to produce the 4,9-diene from this material with bromine in pyridine led to unstable mixtures containing only a little of the desired material (uv analysis).

17β-Acetoxy-16α,17-cyclopropanoestr-4-en-3-one (7, R = Ac).—Hydrolysis of **5** (R = H) according to procedure O followed by acetylation afforded the conjugated ketone: mp 115–117°; 5.70, 5.98 μ.

Anal. Found: C, 76.88; H, 8.64.

Registry No.—**1b** (R′ = Ac; R = Me), 29172-54-1; **1c** (R = Et; R′ = Ac), 29172-55-2; **1e** (R′ = Ac), 29172-56-3; **1e** (R′ = H), 29172-57-4; **1f** (R′ = Ac; R = Me), 29172-58-5; **1f** (R′ = H; R = Me), 29172-59-6; **1f** (R = Et; R′ = Ac), 29172-60-9; **1f** (R = Et; R′ = H), 29172-61-0; **1f** (R = Ac; R′ = Ac), 29172-62-1; **1f** (R, R′ = H), 29172-63-2; **1f** (R = Ac; R′ = H), 29172-64-3; **1f** (Δ^5; R = Ac; R′ = H), 29172-65-4; **1g** (R′ = H), 26729-16-8; **1h** (R′ = Ac; X = Br), 29172-67-6; **1h** (R′ = H; X = Br), 29172-68-7; **1h** (R′ = Ac; X = Cl), 29172-69-8; **1h** (R′ = H; X = Cl), 29172-70-4; **1i** (R′ = H; Z = O), 10458-94-3; **1j** (R′ = Ac; Y = OH), 29172-72-3; **1j** (R′ = Ac; Y = OH), 29172-73-4; **1j** (R′ = H; Y = OH), 29172-74-5; **1j** (R′ = H; Y = OMe), 29172-75-6; **1j** (R′ = Ac; Y = OMe), 29172-76-7; **2e**, 29172-77-8; **2e** (Δ^4), 29172-78-9; **2f** (R = Me), 29172-79-0; **2f** (enol acetate, R = Me), 29172-80-3; **2f** (R = Et), 29172-81-4; **2f** (3-enol acetate; R = Et), 29172-82-5; **2f** (R = Ac), 29172-83-6; **2f** (R = H), 29172-84-7; **2f** (R = Et; 5α-OAc), 29172-85-8; **2f** (R = Et; Δ^4), 29172-86-9; **2f** (R = Ac; 5α-OAc), 29172-87-0; **2f** (R = Ac; Δ^4), 29162-95-6; **2f** (R = H; Δ^4), 29162-96-7; **2g** (5α-OAc), 29162-97-8; **2i** (Z = O), 29162-

(29) W. S. Johnson and W. F. Johns, *J. Amer. Chem. Soc.*, **79**, 2007 (1957).

98-9; **3a** (R′, R″ = OAc), 29246-51-3; **3a** (R′ = H; R″ = Ac), 29162-99-0; **3b** (R = Et; R′, R″ = Ac), 29163-00-6; **3c** (R = Et; R′, R″ = Ac), 29163-01-7; **3c** (R, R′, R″ = Ac), 29163-02-8; **3f** (R = Et; R′, R″ = Ac), 29246-52-4; **3f** (R = Et; R′ = H; R″ = Ac), 29163-03-9; **3f** (R = Et; R′, R″ = H), 29163-04-0; **3f** (R, R′, R″ = H), 29163-05-1; **3f** (R, R′ = H; R″ = Ac), 29163-06-2; **3f** (R, R″ = Ac; R′ = H), 29163-07-3; **3g** (R′ = H; R″ = Ac), 29163-08-4; **3g** (R′, R″ = Ac), 29163-09-5; **4f** (R = Et), 29163-10-8; **4f** (R = Ac), 29163-11-9; **4f** (R = H), 29163-12-0; **4f** (R = $SiMe_3$), 29163-13-1; **4i** (Z = β-OH, H), 29163-14-2; **5** (R = Et), 29163-15-3; **5** (R = $SiMe_3$), 29163-16-4; **6** (R = Et), 29163-17-5; **6** (R = H), 29246-53-5; **6** (R = Ac), 29163-18-6; **7** (R = Et), 29163-19-7; **7** (R = Ac), 29163-20-0; **8**, 29163-21-1; 3,-17-diketo-17-methyl-16,17-secoandrost-4-en-16-oic acid, 29163-22-2; 3β-formyloxyandrost-5-en-17-one, 29163-23-3; 3β,5α-dihydroxyandrostan-17-one 3-formate, 29246-54-6.

Acknowledgment.—The competent technical assistance of Mrs. B. Tucker and Mr. R. Reuter is gratefully acknowledged.

A New Approach to the Synthesis of Nucleosides of 8-Azapurines (3-Glycosyl-*v*-triazolo[4,5-*d*]pyrimidines)[1]

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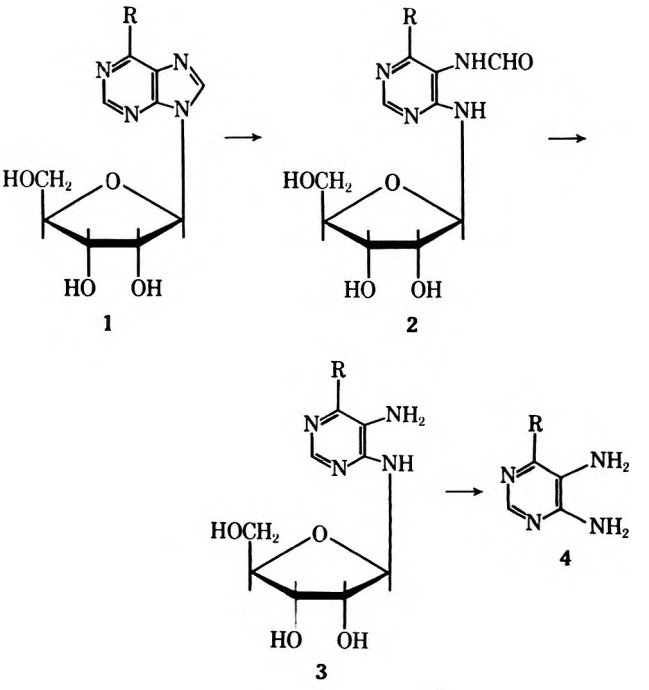
The four isomeric ribosyl derivatives of 8-azahypoxanthine (*v*-triazolo[4,5-*d*]pyrimidin-7(6*H*)-one) have been prepared from appropriately protected derivatives of 6-chloro-9-β-D-ribofuranosylpurine by means of basic cleavage of the imidazole ring of the nucleosides followed by removal of the formyl group from the 5-amino group, closure of the triazole ring with nitrous acid, and then removal of the sugar-protecting groups.

It has been known for some time that certain purines suffer attack by aqueous base at C_2 or C_8, resulting in opening of the pyrimidine[2] or imidazole[3] ring. It appeared to us that these reactions might have synthetic utility, especially in the preparation of 2-[4] and/or 8-azapurine (imidazo[4,5-*d*]-*v*-triazine and *v*-triazolo-[4,5-*d*]pyrimidine) nucleosides difficult to prepare by other methods. For example, the synthesis of 8-azainosine *via* 8-azaadenosine by conventional procedures[6,7] presents difficulties, particularly in the preparation of large amounts of material. One approach to this problem might be to open the imidazole ring of an appropriately substituted purine nucleoside and cyclize the resultant 5-amino-4-glycosylaminopyrimidine with nitrous acid. The possibilities of this route were therefore surveyed.

Inosine (**1**, R = OH), a likely candidate for this route, is quite stable to base,[8] and, although it can be labilized by alkylation at N_7,[9] this approach did not appear promising.[10] Adenosine (**1**, R = NH_2) is completely converted to other compounds in 2 hr by aqueous base at 100°.[11] The only ring-opened product that could be isolated, however, was 4,5,6-triaminopyrimidine (**4**, R = NH_2).[8] Brown and coworkers found that purine ribonucleoside (**1**, R = H)[3] and purine ribonucleotide[12] are extremely sensitive to base, giving rise to sugar-containing pyrimidines that are converted finally to 4,5-diaminopyrimidine (**4**, R = H) (Scheme I). In-

SCHEME I



vestigations in this laboratory[13] and by Brown and coworkers[3] showed that, although 6-chloropurine reacts with aqueous base to give hypoxanthine,[14] nucleosides of 6-chloropurine undergo ring opening under milder

(1) This work, was supported by funds from the C. F. Kettering Foundation and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51. A preliminary account of this work has appeared: J. A. Montgomery and H. J. Thomas, *Chem. Commun.*, 265 (1970).

(2) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 539 (1960).

(3) M. P. Gordon, V. S. Weliky, and G. B. Brown, *J. Amer. Chem. Soc.*, **79**, 3245 (1957).

(4) A synthesis of 2-azaadenosine using this approach has recently been described.[5]

(5) J. A. Montgomery and H. J. Thomas, *Chem. Commun.*, 458 (1969).

(6) J. Davoll, *J. Chem. Soc.*, 1593 (1958).

(7) W. W. Lee, A. P. Martinez, G. L. Tong, and L. Goodman, *Chem. Ind. (London)*, 2007 (1963).

(8) A. S. Jones, A. M. Mian, and R. T. Walker, *J. Chem. Soc.*, 692 (1966).

(9) K. H. Scheit and A. Holy, *Tetrahedron Lett.*, 4303 (1966).

(10) J. A. Montgomery and H. J. Thomas, unpublished data.

(11) J. A. Montgomery and H. J. Thomas, *J. Amer. Chem. Soc.*, **87**, 5442 (1965).

(12) D. I. Magrath and G. B. Brown, *ibid.*, **79**, 3252 (1957).

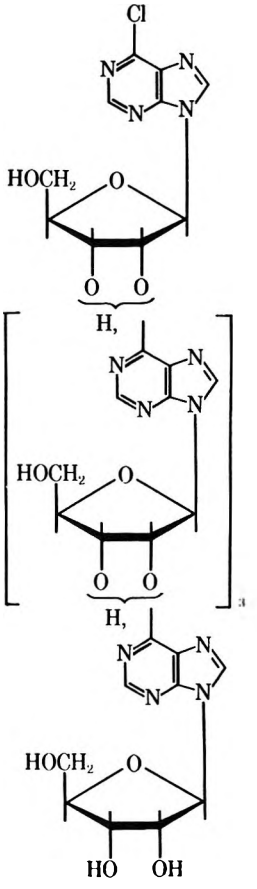
(13) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

(14) A. Bendich, P. J. Russell, and J. J. Fox, *J. Amer. Chem. Soc.*, **76**, 6073 (1954).

conditions than those required for chloro displacement to give compounds tentatively identified on the basis of their ultraviolet spectra as 5-amino-4-chloro-6-glycosylaminopyrimidines, such as **3**.[15] In neither case were the products actually isolated and identified. In the related case referred to above, Brown and coworkers[3] found that purine ribonucleoside is facilely cleaved by base primarily to two 5-amino-4-ribosylaminopyrimidines as judged by chromatography and ultraviolet spectroscopy, but the nature of the ribosyl moiety was not determined.

In relevant synthetic work, Todd and coworkers[17] found that they could prepare adenosine by the basic ring closure of 4-amino-6-[(2,3-di-*O*-acetyl-5-*O*-benzyl-D-ribofuranosyl)amino]-5-thioformamido-2-(methylthio)pyrimidine followed by the reductive removal of the 5′-*O*-benzyl and the 2-methylthio group. None of the α anomer of adenosine was detected. A similar synthesis of 9-D-ribopyranosyladenine gave the β anomer, and it was concluded that the intermediate 4-D-ribopyranosylaminopyrimidines also had the β configuration.[18,19]

We decided to study the effect of aqueous base on 6-methoxypurine ribonucleoside (**1**, R = OCH_3) and 6-(methylthio)purine ribonucleoside (**1**, R = SCH_3), in addition to 6-chloropurine ribonucleoside (**1**, R = Cl). The 6-methoxypurine ribonucleoside (**1**, R = OCH_3) was completely converted to inosine (**1**, R = OH), and no ring cleavage resulted. The 6-(methylthio)purine ribonucleoside (**1**, R = SCH_3) did undergo ring cleavage but much more slowly than 6-chloropurine ribonucleoside (**1**, R = Cl), and the conditions necessarily employed caused rupture of the glycosyl linkage so that the major product of the reaction was 4,5-diamino-6-(methylthio)pyrimidine (**4**, R = SCH_3). These results caused us to concentrate our attention on the reaction of 6-chloropurine ribonucleoside (**1**, R = Cl) with base. The alkaline hydrolysis of **1** (R = Cl) described above[3] was carried out in very dilute solution. When we increased the concentration of substrate, a quite different result obtained: a very insoluble white solid precipitated from solution. The ultraviolet spectrum of this material was similar to that of 6-methoxypurine, but little could be concluded from its pmr spectrum. More vigorous treatment of this material with base gave inosine (**1**, R = OH). It is, therefore, apparent that 6-chloropurine ribonucleoside (**1**, R = Cl) polymerized by attack of the anion of one of the sugar hydroxyls on C_6. The polymeric material failed to give the typical metaperiodate–Schiff test for cis hydroxyls[20] and, thus, either the 2′- or 3′-hydroxyl must be involved. Since, in other cases, attack is known to occur at the 2′-hydroxyl of **1** (R = Cl),[21] we believe the linkage is between C_6 and C_2′. Elemental analyses indicated that the polymer is likely a pentamer (**5**). A variety of conditions gave the same material.



5

Because this difficulty could obviously be circumvented by protecting the sugar moiety with a base-stable group, we next studied the effect of base on 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (**6**). Hydrolysis of **6** with 0.5 *N* sodium hydroxide in dioxane–water (1:1) at room temperature for 45 min gave a 7.6% yield of 2′,3′-*O*-isopropylideneinosine (**7**), a quite unexpected product (hypoxanthine nucleosides were undetected by previous workers), and a 47% yield of 4-chloro-5-formylamino-6-[(2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (**8**) (Scheme II). Although the ultraviolet spectra of the reaction mixtures obtained by the previous investigators led them to conclude that the products were the 5-amino-4-chloro-6-glycosylaminopyrimidines,[3,13] we found no compound of this type. In truth, however, this earlier data[3,13] is not really consistent with that for either structure (see Table I), due no doubt to the fact that the reaction gave at least three products (see below). An examination of the pmr spectrum of the formylaminopyrimidine **8**, in conjunction with that of **17** (see Experimental Section), established that the sugar had retained its β-D-ribofuranosyl configuration.

It was now necessary to remove the formyl group in order to effect ring closure to the triazolo[4,5-*d*]pyrimidine ribonucleoside. We were unable to find conditions under which we could, by means of aqueous base, remove the formyl group from **8** without also rupturing the glycosyl linkage giving 4,5-diamino-6-chloropyrimidine (**4**, R = Cl). These results, along with the ultraviolet spectra of all the compounds involved (Table I),

(15) In contrast to the nucleosides, 9-ethyl-6-chloropurine was converted to 9-ethylhypoxanthine by aqueous base,[16] indicating that substitution at N-9 is not the determining factor but that the nature of the substituent is.

(16) J. A. Montgomery and C. Temple, Jr., *J. Amer. Chem. Soc.*, **79**, 5238 (1957).

(17) G. W. Kenner, C. W. Taylor, and A. B. Todd, *J. Chem. Soc.*, 1620 (1949).

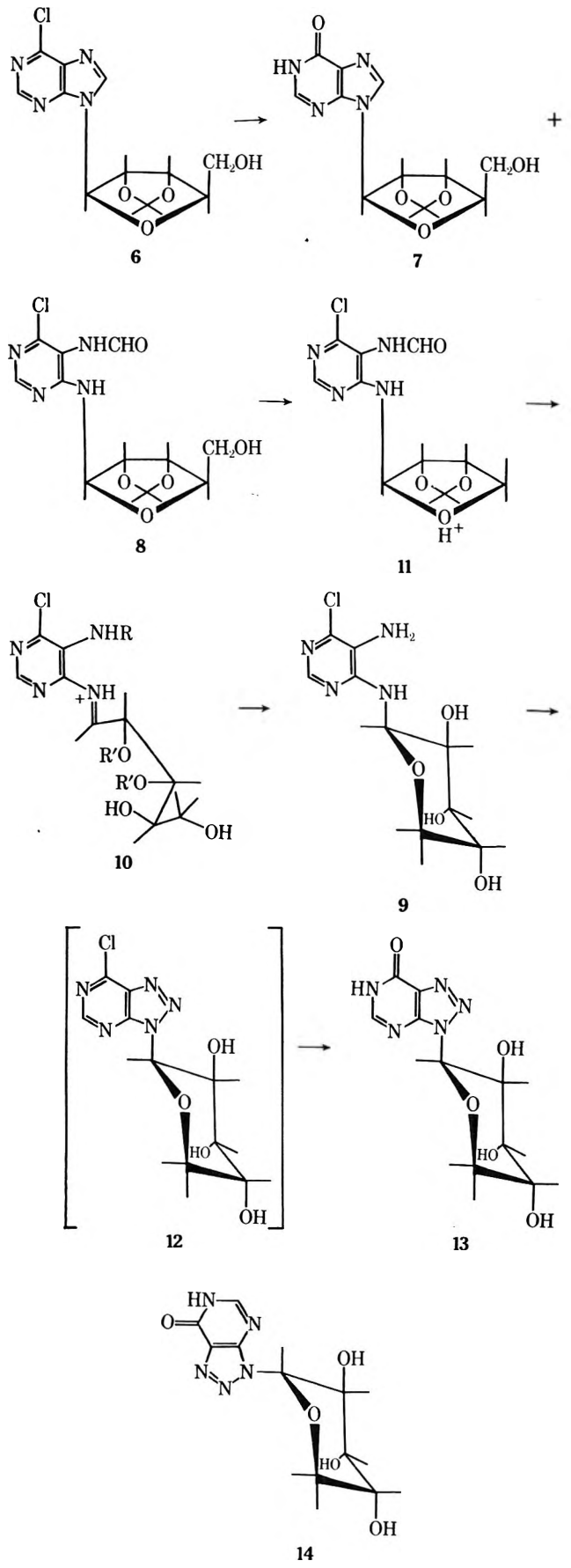
(18) G. A. Howard, G. W. Kenner, B. Lythgoe, and A. R. Todd, *ibid.*, 855 (1946).

(19) G. W. Kenner, H. J. Rodd, and A. R. Todd, *ibid.*, 1613 (1949).

(20) Although trans-vicinal hydroxyls also give a positive test, the rate of oxidation is much slower and the intensity of the color developed is less.

(21) T. A. Khwaja and R. K. Robins, *J. Amer. Chem. Soc.*, **88**, 3640 (1966).

SCHEME II



indicate that Brown and coworkers[3] probably obtained a mixture of inosine (1, R = OH), 4-chloro-5-formylamino-6-(β-D-ribofuranosyl)aminopyrimidine (2, R = Cl), and 4,5-diamino-6-chloropyrimidine (4, R = Cl), but none of the 5-amino-4-chloro-5-(β-D-ribofuranosyl)-aminopyrimidine (3, R = Cl) that we desired.

Treatment of 8 with hydrochloric acid readily removed the formyl and isopropylidene groups, but the resultant product was shown by chromatography to be a mixture of two compounds, which were not separated but were treated with sodium nitrite in the aqueous acid. This treatment resulted in closure to the *v*-triazolo[4,5-*d*]pyrimidine 12, followed by hydrolysis of the now labile chlorine of 12[22] to give 13. The major product isolated from this reaction was identified on the basis of its spectra (*vide infra*) and elemental analyses as 9-β-D-ribopyranosyl-8-azahypoxanthine (13); the minor component was identified in the same way as the α anomer 14. The acid treatment[23] obviously opened the furanose ring to give a structure such as 10,[25] which then reclosed to the pyranose 9.[27] The nature of the sugar moiety of 9 should be determined by the relative stabilities of the possible isomers. The pyranoses are in general more stable than the furanoses.[28] The most stable isomer of the final product (and hence of 9) should be the β-pyranose in the normal (*N*) conformation (13).[29,30] In this conformation the $C_{1'}$ and $C_{2'}$ protons would be trans diaxial. The coupling constant $J_{1'2'}$ of 13 is 9.5 Hz (see Table II), which indicates[31] that, indeed, this compound is the β anomer and, therefore, that ring closure of 9 gave primarily the β anomer 12, which exists principally in the *N* conformation. The $C_{1'}$ and $C_{2'}$ protons of the α-pyranose (14) would be cis axial–equatorial in either the *N* or the *A* conformation and therefore, the coupling constant $J_{1'2'}$ cannot be used to distinguish between the two conformers. Both of these conformers have instability factors.[32] In the *N* conformation the bulky 8-azapurine moiety is axial, and it would seem that under conditions of the ring closure the anomeric effect[33] might not be significant. On the other hand, the *A* conformation would have 1,3-diaxial hydroxyls, and the Δ2 effect[34] would be operative. The chemical shift of the $C_{1'}$ proton of 14 would support, but not establish, the *N* conformation since the absorption band is downfield from that of the β-pyranose 13.[35]

In order to prevent this furanose–pyranose isomerization, we sought a blocking group for the 5′-hydroxyl that would withstand both the basic ring cleavage and the acidic amide hydrolysis steps, but which could later be removed from the 8-azapurine ribonucleoside. The

(22) Y. F. Shealy, J. D. Clayton, C. A. O'Dell, and J. A. Montgomery, *J. Org. Chem.*, **27**, 4518 (1962).

(23) Under conditions similar to those used originally for the amide hydrolysis, *i.e.*, methanolic hydrochloric acid, Bishop and Cooper[24] found that the equilibrium mixture of *O*-methyl glycosides formed from ribose consisted of 65.8% β-pyranose, 17.4% β-furanose, 11.6% α-pyranose, and 5.2% α-furanose.

(24) C. T. Bishop and F. P. Cooper, *Can. J. Chem.*, **41**, 2743 (1963).

(25) This reaction is similar to the first step in the acid-catalyzed hydrolysis of *N*-arylglycosylamines.[26]

(26) B. Capon and B. E. Connett, *Tetrahedron Lett.*, 1395 (1964).

(27) It is not known whether the isopropylidene group, which might well influence this reaction, comes off before or after reclosure.

(28) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1956, p 378.

(29) Z. Samek and J. Farkas, *Collect. Czech. Chem. Commun.*, **30**, 2149 (1965).

(30) Y. H. Pan, R. K. Robins, and L. B. Townsend, *J. Heterocycl. Chem.*, **4**, 246 (1967).

(31) L. D. Hall, *Advan. Carbohyd. Chem.*, **19**, 51 (1964).

(32) Reference 28, p 371.

(33) Reference 28, p 375.

(34) Reference 28, p 377.

(35) R. U. Lemieux and J. D. Stevens, *Can. J. Chem.*, **44**, 249 (1966).

TABLE I

ULTRAVIOLET SPECTRAL DATA

Compd	0.1 N HCl Max, nm (ε × 10⁻³)	0.1 N HCl Min, nm	pH 7 buffer Max, nm (ε × 10⁻³)	pH 7 buffer Min, nm	0.1 N NaOH Max, nm (ε × 10⁻³)	0.1 N NaOH Min, nm
8	240 (12.9)	<225	239 (12.8)	<225	258 (sh) (9.24)	232
	273 (5.7)	264	273 (5.5)	263	280 (9.68)	265
Reaction mixture[a]	250.5	*Ca.* 230			254	*Ca.* 232
	292	*Ca.* 275			290	274
Reaction mixture[b]	*Ca.* 260					
	307					
9	*Ca.* 275 (sh)	244	255	229	256	230
	302		291	270	291	270
4, R = Cl	269	237	254	228	253	230
	307	280	290	269	290	269
4-Amino-6-chloro-5-formylaminopyrimidine[c]	237 (8.2)	220	237 (9.6)	219	256.5 (7.0)	231
	278 (4.5)	260	278.5 (4.0)	258	283.5 (7.0)	270
13	254 (9.83)	224	255 (8.68)	226	275 (10.5)	229
14	254 (9.10)	227	255 (8.04)	228	275 (9.94)	230
α-21	254 (8.82)	228	256 (8.58)	230	275 (9.82)	232
β-21	255 (9.8)	228	255 (8.85)	228	276 (10.9)	232

[a] See ref 3. [b] See ref 13. [c] J. A. Montgomery and K. Hewson, *J. Org. Chem.*, **26**, 4469 (1961).

TABLE II

PMR SPECTRAL DATA

Compd	C_1' H, δ in ppm	$J_{1'2'}$, Hz	CH_2OH, δ in ppm
13	5.86	9.8	
14	6.07	2.2	
β-21	6.11	5.0	3.55
β-22	6.25	2.0	3.48
α-21	6.56	6.2	3.50
α-22	6.60	5.0	3.66

urethane group was selected and 6-chloro-9-[2,3-*O*-isopropylidene-5-*O*-(*m*-chlorophenylcarbamoyl)-β-D-ribofuranosyl]purine (**15**) was prepared by the reaction of **6** with *m*-chlorophenyl isocyanate (Scheme III). Treatment of **15** with aqueous base gave results similar to those obtained with **6**; a 44% yield of 4-chloro-5-formylamino-6-[(2,3-*O*-isopropylidene-5-*O*-(*m*-chlorophenylcarbamoyl)-β-D-ribofuranosyl)amino]pyrimidine (**17**) was obtained. This compound, on treatment with methanolic hydrochloric acid, gave four products, two of which had retained the isopropylidene group (**19**) and two of which had not (**18**), as judged by the metaperiodate–Schiff test and their chromatographic behavior. Treatment of **18** with aqueous nitrous acid followed by methanolic methoxide gave 8-azainosine (**β-21**)[6] and its α anomer (**α-21**), resulting from ring closure of **18** followed by hydrolysis of the chloro group and then cleavage of the urethane **20**. Treatment of **19** in the same way gave the isopropylidene derivatives of 8-azainosine and its α anomer (**α-** and **β-22**). Acid hydrolysis converted **22** into **α-** and **β-21**.

An examination of the pmr spectra of these compounds (Table II) confirms their identity. Of particular interest are the coupling constants for C_1' H and C_2' H of the anomeric pair **α-** and **β-22**. The presence of the isopropylidene group lowers the coupling constant $J_{1'2'}$ of the β anomer from 5.0 Hz to 2.0 Hz in agreement with findings of previous workers.[36,37] The pmr spectra of few isopropylidene derivatives of α-ribonucleosides have been examined. In the case of **α-22** the coupling constant $J_{1'2'}$ is only lowered from 6.0 to 5.0 Hz, indicating a dihedral angle of 37.5° (Karplus equation), easily accommodated by the cis protons of the α anomer. In addition, the bands due to the C_1' H of the α anomers are downfield from those of the β anomers.[38,39] No exceptions to this empirically satisfactory rule have yet been found.

The yield of **α-21** was slightly higher than that of **β-21**, indicating no great difference in the stability of **α-** and **β-18** or of **α-** and **β-19**, in contrast to the pyranoses. Even the presence of the isopropylidene group of **19** does not appear to favor closure to the β anomer.

Thus, by the use of appropriate blocking groups, we have been able to prepare all four isomeric ribonucleosides of 8-azahypoxanthine (**13**, **14**, and **α-** and **β-20**) from 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (**6**). The stability of 8-azainosine (**β-21**) and its pyranose isomer (**13**) to both acid and base was examined. The furanose isomer **β-20** is more labile to both, and in each case the nucleoside is cleaved to 8-azahypoxanthine.

Experimental Section

The melting points reported were determined with a Mel-Temp apparatus and are not corrected. The optical rotations were determined in the solvents specified with a Rudolph Model 80 polarimeter. The uv spectra were determined in aqueous solution with a Cary Model 14 spectrophotometer. The ir spectra of the compounds were determined in pressed KBr disks with a Perkin-Elmer Model 521 spectrophotometer but are not reported. The pmr spectra (Table II) were determined in DMSO-d_6 containing TMS as internal reference with a Varian A-60A spectrometer. Chromatographic analyses were carried out on thin layer plates of silica gel H (Brinkmann). The plates were developed in mixtures of $CHCl_3$ and MeOH in various proportions. The spots were detected by uv light after spraying the plates with Ultraphor (WT, highly concentrated) (BASF Colors & Chemicals, Inc., Charlotte, N. C.). Most of the chromatographic purifications were carried out on Mallinckrodt SilicAR-7 with the solvents indicated. The analytical samples were dried over P_2O_5 at 0.07 mm for 16–20 hr at the temperatures given.

Polymer of 6-Chloro-9-β-D-ribofuranosylpurine (5).—A solution of 6-chloro-9-β-D-ribofuranosylpurine (574 mg, 2.00 mmol) in

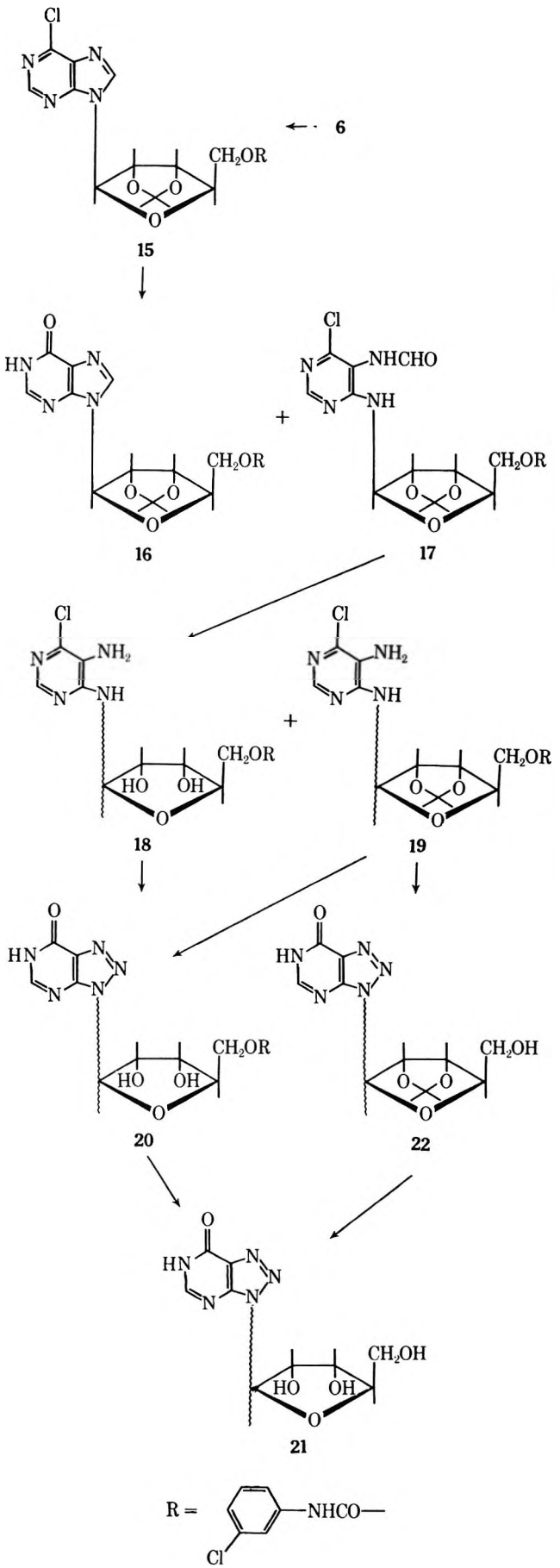
(36) N. J. Leonard and R. A. Laursen, *J. Amer. Chem. Soc.*, **85**, 2026 (1963).

(37) J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, **34**, 2646 (1969).

(38) J. A. Montgomery and H. J. Thomas, *J. Amer. Chem. Soc.*, **87**, 5402 (1965).

(39) T. Nishimura and B. Shimizu, *Chem. Pharm. Bull.*, **13**, 803 (1965).

SCHEME III



0.1 *N* KOH (40 ml) was heated at 50° for 1 hr. The precipitate that formed was collected by filtration and washed with H_2O, yield 320 mg (61%).

The analytical sample was obtained by precipitation from DMF–EtOH. It was dried at 100°: λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl 254 (49.2); pH 7 254 (49.1); 0.1 *N* NaOH 253 (50.8).

Anal. Calcd for $C_{50}H_{51}ClN_{20}O_{20}\cdot 2H_2O$: C, 45.37; H, 4.19; N, 21.16; Cl, 2.75. Found: C, 45.50; H, 4.20; N, 21.13; Cl, 2.43.

4-Chloro-5-formylamino-6-[(2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (8).—To a cold solution of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (6.00 g, 18.4 mmol) (6) in dioxane (110 ml) was added cold 1 *N* NaOH solution (110 ml). The resulting solution was kept at room temperature for 45 min, stirred with Amberlite IR-120 (H) ion exchange resin until a pH of 4–5 was obtained, filtered to remove the resin, basified to pH 8 with concentrated NH_4OH, and then evaporated to dryness *in vacuo*. During the evaporation, *n*-BuOH was added at intervals to prevent foaming. The residue crystallized from methanol, yield 2.06 g.

The residue from evaporation of the mother liquor was purified by preparative tlc, $CHCl_3$–MeOH (95.5). This treatment gave another 900 mg of product 8 (total yield, 47%) and 215 mg (7.6%) of 2′,3′-*O*-isopropylideneinosine (7).

The analytical sample of the product was obtained by recrystallization from MeOH. It was dried at 78°: mp 180–181°; δ 1.3 and 1.5 (2 s, CH_3), 3.5 (m, $C_{5'}$ H_2), 4.8 (m, $O_{5'}$ H, $C_{2'}$ H, and $C_{3'}$ H), 6.0 (m, $C_{1'}$ H), 6.5 (m, N_6 H), 8.4 (m, C_2 H and CHO), 9.8 ppm (broad, N_5 H). Addition of D_2O to the DMSO-d_6 solution replaced the NH and OH protons by deuterium, and this resulted in collapse of the multiplet at 6.0 ppm to a triplet rather than the expected doublet, apparently due to virtual coupling between $C_{1'}$ H and $C_{3'}$ H. The small coupling constants of this triplet (2 Hz) confirm that 8 is a β-*N*-glycoside.

Anal. Calcd for $C_{13}H_{17}ClN_4O_5$: C, 45.29; H, 4.97; N, 16.25. Found: C, 45.12; H, 4.98; N, 16.17.

9-β- and -α-D-Ribopyranosyl-8-azahypoxanthine (13 and 14). A.—A solution of 4-chloro-5-formylamino-6-[(2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (910 mg, 2.65 mmol) (8) in MeOH (90 ml) was treated with MeOH (26.3 ml) containing concentrated HCl (0.22 ml), and the resulting solution was refluxed 30 min, neutralized to pH 5 with a concentrated NH_4OH solution, and then evaporated to dryness *in vacuo*. The white glass that was obtained was shown by tlc to be a mixture of two major products.

A solution of this mixture in H_2O (50 ml) was chilled in an ice bath and acidified with glacial HOAc (1 ml). To the resulting solution was added dropwise a solution of $NaNO_2$ (730 mg, 10.6 mmol) in H_2O (4.0 ml). The reaction solution was kept in the ice bath for 10 min and then left at room temperature for 20 hr. It was then basified to pH 10 with a concentrated NH_4OH solution, and a solution of $Pb(OAc)_2\cdot 3H_2O$ (1.53 g, 4.05 mmol) in H_2O (10 ml) was added. The resulting precipitate was collected by filtration and dissolved in 20% HOAc (v/v) (10 ml). Treatment of the solution with H_2S for 2 min gave a precipitate of PbS that was removed by filtration. Evaporation of the filtrate to dryness gave a mixture of the α- and β-D-ribopyranoses of 8-azahypoxanthine as a white glass. The β anomer crystallized from a solution of the mixture in 80% EtOH, yield 80 mg.

The analytical sample (13) was obtained by recrystallization from 80% EtOH. It was dried at 78°: mp 266–267° dec; $[\alpha]^{24}D$ −44.6 ± 1.2° (*c* 0.52, H_2O).

Anal. Calcd for $C_9H_{11}N_5O_5$: C, 40.15; H, 4.12; N, 26.01. Found: C, 40.11; H, 4.13; N, 25.95.

Evaporation of the mother liquor gave a residue that was purified by preparative tlc using $CHCl_3$–MeOH (9:1) as the developing solvent. The two major bands obtained were eluted with boiling MeOH. The faster-moving material was more of the β anomer, yield 95 mg (total yield 24%). The slower-moving material was the α anomer, yield 135 mg (19%).

The analytical sample of the α anomer 14 was obtained by purification through the lead salt as a white solid. It was dried at 100°: melting point indefinite; $[\alpha]^{24}D$ −52.4 ± 1.5° (*c* 0.90, H_2O).

Anal. Calcd for $C_9H_{11}N_5O_5$: C, 40.15; H, 4.12; N, 26.01. Found: C, 40.26; H, 4.11; N, 25.81.

B.—A solution of 4-chloro-5-formylamino-6-[(2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (1.19 g, 3.45 mmol) (8) in 0.1 *N* HCl (70 ml) was left at room temperture for 20 hr and then chilled in an ice bath. The cold solution was then stirred while a solution of $NaNO_2$ (953 mg, 13.8 mmol) in H_2O (5 ml) was slowly added. The resulting solution was stirred for 10 min, refrigerated for 24 hr, then taken to pH 10 with concentrated

NH_4OH, and treated with $Pb(OAc)_2 \cdot 3H_2O$ (2.01 g, 5.3 mmol) in H_2O (10 ml). The precipitate that formed was collected by filtration and washed thoroughly with H_2O. A solution of the resulting solid in 20% aqueous HOAc (25 ml) was treated with H_2S until there was no longer a precipitate of PbS. The black precipitate was filtered and washed thoroughly with H_2O. The combined filtrate and wash was evaporated to dryness *in vacuo*. From an aqueous solution of the residue there was obtained the β anomer as a crystalline solid, yield 85 mg. Purification of the filtrate by preparative tlc gave another 186 mg of β anomer (total yield 271 mg, 23%) and 170 mg (18%) of α anomer.

6-Chloro-9-[5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl]purine (15).—A solution of 6-chloro-9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)purine (1.96 g, 6.0 mmol) (6), triethylamine (0.84 ml, 6.0 mmol), and 3-chlorophenyl isocyanate (1.46 ml, 12.0 mmol) in DMF (35 ml) was held for 20 hr at room temperature and then evaporated to dryness *in vacuo*. A solution of the residue in ether yielded 729 mg (2.5 mmol) of crystalline 3,3′-dichlorocarbanilide. The filtrate was evaporated to dryness *in vacuo*. The residue thus obtained crystallized from MeOH, yield 2.42 g (88%).

A small sample was recrystallized from MeOH for analysis. It was dried at 78°: mp 96–100°; λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl 238 (15.3), 265 (7.34); pH 7 238 (15.1), 265 (7.28); 0.1 *N* NaOH 239 (14.8), 264 (8.50).

Anal. Calcd for $C_{20}H_{19}Cl_2N_5O_5$: C, 50.01; H, 3.99; N, 14.58. Found: C, 50.21; H, 3.96; N, 14.64.

4-Chloro-5-formylamino-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (17).—To a solution of 6-chloro-9-[5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl]purine (480 mg, 1.00 mmol) (15) in dioxane (6 ml) was added 1 *N* NaOH (6 ml). The resulting cloudy suspension became clear after stirring 10 min at room temperature. The clear solution was held an additional 45 min. It was then chilled in an ice bath and slowly neutralized with concentrated HCl. The mixture was evaporated to dryness *in vacuo*, and the residue was partitioned between $CHCl_3$ and H_2O (100 ml each). The $CHCl_3$ layer was dried over $MgSO_4$ and then evaporated to dryness. The residue crystallized from EtOH, yield 220 mg (44%). Addition of D_2O to the DMSO-d_6 solution replaced the NH protons by deuterium, and this resulted in collapse of the doublet of doublets at 6.0 ppm to the expected doublet with a coupling constant of 4 Hz.

The analytical sample was obtained by recrystallization from EtOH. It was dried at 78°: mp 169°; λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl 237 (24.8), 273 (6.20); pH 7 237 (24.8), 273 (6.00); 0.1 *N* NaOH 239 (16.8), 275 (sh) (10.8); δ 1.4 and 1.5 (2 s, CH_3), 4.2 (m, C_4' H and C_5' H_2), 4.9 (m, C_2' H and C_3' H), 6.0 (m, C_1' H), 6.6 (d, N_6 H), 7.1, 7.3, and 7.6 (m, phenyl H), 8.4 (s, C_2H and CHO), 9.9 ppm (s, broad, 2 H of NHCO).

Anal. Calcd for $C_{20}H_{21}Cl_2N_5O_6$: C, 48.21; H, 4.25; N, 14.05; Cl, 14.23. Found: C, 48.47; H, 4.20; N, 14.14; Cl, 14.26.

In another run a 3% yield of 5′-*O*-(*m*-chlorophenylcarbamoyl)-2′,3′-*O*-isopropylideneinosine (16) was isolated by thin layer chromatography.

Deformylation of 4-Chloro-5-formylamino-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine.—A solution of 4-chloro-5-formylamino-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl)amino]pyrimidine (999 mg, 2.00 mmol) in 0.017 *N* methanolic HCl (120 ml) was refluxed for 30 min, neutralized to pH 5 with concentrated NH_4OH, and then evaporated to dryness *in vacuo*. Trituration of the residue with H_2O produced a solid weighing 867 mg. Purification by preparative tlc using $CHCl_3$–MeOH (95:5) as the developing solvent gave three major bands. Each band was eluted with boiling MeOH. Evaporation of the MeOH solutions gave the following products: 5-amino-4-chloro-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-α- and -β-D-ribofuranosyl)-amino]pyrimidine (18), 310 mg (36%); 5-amino-4-chloro-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene)-α- and -β-D-ribofuranosyl)amino]pyrimidine (19), 284 mg (30%); and starting material 17, 129 mg (13%).

8-Azainosine (β-21).—A solution of 2′,3′-*O*-isopropylidene-8-azainosine (β-22) in 0.1 *N* H_2SO_4 (20 ml) was kept at room temperature for 3 days, neutralized with $Ba(OH)_2$ solution, filtered to remove the precipitate of $BaSO_4$, and evaporated to dryness *in vacuo*. The residue crystallized from 80% aqueous EtOH, yield 14 mg (41%). The uv and ir spectra of this material were identical with that of an authentic sample of 8-azainosine.[6]

9-α-D-Ribofuranosyl-8-azahypoxanthine (α-21).—A solution of the α anomer of 2′,3′-*O*-isopropylidene-8-azainosine (70 mg, 0.23 mmol) (α-22) in 0.1 *N* H_2SO_4 (40 ml) was left for 24 hr at room temperature, neutralized with $Ba(OH)_2$ solution, filtered to remove the precipitate of $BaSO_4$, and evaporated to dryness *in vacuo*. The residue was dissolved in H_2O (2 ml), and the solution made basic (pH 10) with concentrated NH_4OH. A solution of $Pb(OAc)_2 \cdot 3H_2O$ (349 mg, 0.92 mmol) in H_2O (3 ml) was added. The precipitate that formed was collected by filtration (55 mg). A solution of the lead salt in 20% HOAc (v/v) (20 ml) was treated with H_2S for 2 min, filtered to remove the precipitate of PbS, and evaporated to dryness *in vacuo*. A white solid was obtained. It was dried at 100°: yield 20 mg (29%); $[\alpha]^{24}D$ +119.6 ± 1.2° (*c* 0.53, H_2O).

Anal. Calcd for $C_9H_{11}N_5O_5 \cdot {}^1/_3H_2O$: C, 39.28; H, 4.27; N, 25.44. Found: C, 39.22; H, 4.30; N, 25.32.

8-Azainosine (β-21) and Its α Anomer (α-21).—A solution of 5-amino-4-chloro-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-α- and -β-D-ribofuranosyl)amino]pyrimidine (267 mg, 0.62 mmol) (18) in H_2O (5 ml) and glacial HOAc (2 ml) was chilled in an ice bath while a solution of $NaNO_2$ (172 mg, 2.49 mmol) in H_2O (2 ml) was slowly added. The cloudy solution that resulted cleared on addition of another 2 ml of HOAc. After being stirred in the cold for 15 min, it was refrigerated 20 hr, and then evaporated to dryness. After trituration with H_2O and then ether, the residue became a solid, yield 140 mg (54%).

A solution of the solid [5′-*O*-(*m*-chlorophenylcarbamoyl)-8-azainosine and its α anomer] (121 mg, 0.28 mmol) (20) in 0.1 *N* $NaOCH_3$ in MeOH (10 ml) was refluxed for 4 hr, neutralized with HOAc, and evaporated to dryness *in vacuo*. A solution of the residue in H_2O (10 ml) was made basic (pH 10) with concentrated NH_4OH, and a solution of $Pb(OAc)_2 \cdot 3H_2O$ (190 mg, 0.5 mmol) in H_2O (1 ml) was added. The precipitate that resulted was collected by filtration and dissolved in 20% HOAc (v/v) (10 ml). H_2S was bubbled through the solution for 2 min, and the resulting precipitate of PbS was removed by filtration. Evaporation of the filtrate to dryness gave a hygroscopic solid weighing 43 mg. Purification of this material by preparative tlc, using $CHCl_3$–MeOH (3:1) as the developing solvent, gave a white solid, yield 27 mg (36%). Examination of this material by pmr showed that it was a 1:1 mixture of 8-azainosine (β-21) and its α anomer α-21.

2′,3′-*O*-Isopropylidene-8-azainosine and Its α Anomer (22).—To a cold solution of 5-amino-4-chloro-6-[(5-*O*-(*m*-chlorophenylcarbamoyl)-2,3-*O*-isopropylidene)-α- and -β-D-ribofuranosyl)amino]pyrimidine (280 mg, 0.60 mmol) (19) in glacial HOAc (2 ml) was added a saturated aqueous solution of $NaNO_2$ (180 mg, 2.61 mmol). A precipitate immediately formed, but the addition of HOAc (2 ml) produced a clear solution, which was left 20 hr at room temperature before it was evaporated to dryness *in vacuo*. The residue was partitioned between $CHCl_3$ and H_2O (50 ml each). The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated to dryness *in vacuo*. A yellow glass was obtained: yield 230 mg (85%); λ_{max} nm ($\epsilon \times 10^{-3}$) 0.1 *N* HCl 238 (16.8), 262 (sh) (7.84); pH 7 238 (16.4), 263 (sh) (7.34); 0.1 *N* NaOH 237 (14.2), 276 (9.77).

A solution of this yellow glass [a mixture of 5′-*O*-(*m*-chlorophenylcarbamoyl)-2′,3′-*O*-isopropylidene-8-azainsine and its α anomer] in 0.1 *N* methanolic $NaOCH_3$ (20 ml) was refluxed 1 hr, neutalized with glacial HOAc, and evaporated to dryness *in vacuo*. The residue, a 1:1 mixture of 2′,3′-*O*-isopropylidene-8-azainosine and its α anomer 22, was separated by preparative tlc, using $CHCl_3$–MeOH (9:1) as the developing solvent. The bands were eluted with boiling MeOH. The slower-moving α anomer was obtained as a white solid, yield 70 mg (45%). The β anomer was also a white solid, yield 40 mg (26%).

Registry No.—**4** (R = Cl), 4316-98-7; **5**, 29351-03-9; **8**, 29168-69-2; **9**, 29168-70-5; **13**, 29168-71-6; **14**, 29168-72-7; **15**, 29168-73-8; **17**, 29168-74-9; **α-21**, 28234-86-8; **β-21**, 4968-68-7; **α-22**, 29246-45-5; **β-22**, 29168-77-2.

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Studies on Chrysanthemic Acid. VII.[1] Thermal Decomposition of Chrysanthemyl Oxalate and Deamination of Chrysanthemylamine

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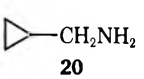
The liquid-phase thermal decomposition of *trans*-chrysanthemyl oxalate (**4**) afforded artemisia triene (**9**) in moderate yields, together with small amounts of oxalic acid under milder conditions (at 160°) compared with those reported for oxalates of general primary and secondary alcohols. The decomposition in the presence of hydroquinone gave similar yields of **9**, but in quinoline the yield was much lower. These results suggested an ion-pair mechanism for the decompositions. Deamination of *trans*-chrysanthemylamine (**7**) with isoamyl nitrite–acetic acid in benzene yielded **9** (38%), chrysanthemyl acetate (**8**) (29.8%), and artemisia acetate (**16**) (27.3%). No appreciable difference between *trans*- (**7**) and *cis*-amine **18** was observed in the product distributions.

Much attention has been paid recently to cyclopropane ring opening reactions induced by a variety of intermediates involving cation, anion, radical, and carbene, etc.[2] Particularly, carbonium ion promoted reactions have been extensively studied[3] with respect to the classical or nonclassical character[4] and the bisected, bicyclobutonium or homoallylic structure[5] of the intermediates. Related examples are found in acid-catalyzed dehydration of cyclopropyl carbinols, solvolysis of cyclopropylcarbinyl esters and halides, deamination of cyclopropylcarbinylamines, and acid-catalyzed rearrangement of cyclopropylcarbinyl ketones. Substituent effects have been investigated by using a number of alkyl- and arylsubstituted cyclopropylcarbinyl systems.[6] Nevertheless, the 2-vinylcyclopropylcarbinyl system has not been reported yet. This paper deals with the results of thermal decomposition of *trans*-chrysanthemyl (2,2-dimethyl-3-isobutenylcyclopropyl-carbinyl) oxalate (**4**) and deamination of *trans*- (**7**) and *cis*-chrysanthemylamine (**18**). The chrysanthemyl system can be regarded as a model to test the isobutenyl substituent effect on cyclopropane ring opening reactions.[7]

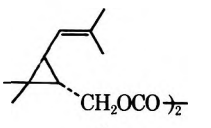
1, R = COOH
2, R = COOEt
3, R = CH_2OH
5, R = COCl
6, R = $CONH_2$
7, R = CH_2NH_2
8, R = CH_2OAc
17, R = CH_2OTs

18, R = CH_2NH_2
19, R = CH_2OAc



20

3 $\xrightarrow{(COCl)_2/\text{pyridine}}$



4

Results and Discussion

Thermal Decomposition of 4.—Treatment of *trans*-chrysanthemol (**3**) with oxalyl chloride in pyridine gave **4** as a colorless oil after chromatography on alumina. The structure was confirmed by analysis and spectral data. This might provide the first example of the successful preparation of a cyclopropylcarbinyl oxalate, since dimethylcyclopropylcarbinol has been reported to give only a rearranged oxalate, and dicylopropylmethyl- and tricyclopropylcarbinols do not react with oxalyl chloride.[8]

Thermolysis of **4** was carried out by heating neat under nitrogen and the resulting products were distilled off directly into a cold trap at *ca.* 0°. Decomposition occurred instantly at 160° under atmospheric pressure affording a volatile colorless oil which contained a small amount of oxalic acid. This oil was shown to be largely artemisia triene (**9**) (2,5,5-trimethyl-1 3,6-heptatriene) by spectroscopic and glpc comparison with an authentic specimen.[9] **9** gave a known maleic anhydride adduct[10] and a nitrosobenzene adduct **10**, confirming the above assignment (Scheme I). The results under several conditions are summarized in Table I.

For the thermal decomposition of oxalates, three distinct reaction paths, *i.e.*, an ion-pair,[11] a free-radical,[12] and a concerted mechanism[13] have been suggested. In the present case, the sole hydrocarbon product **9** is different from the Hofmann degradation of chrysanthemyltrimethylammonium hydroxide (**13**) which has

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SCHEME I

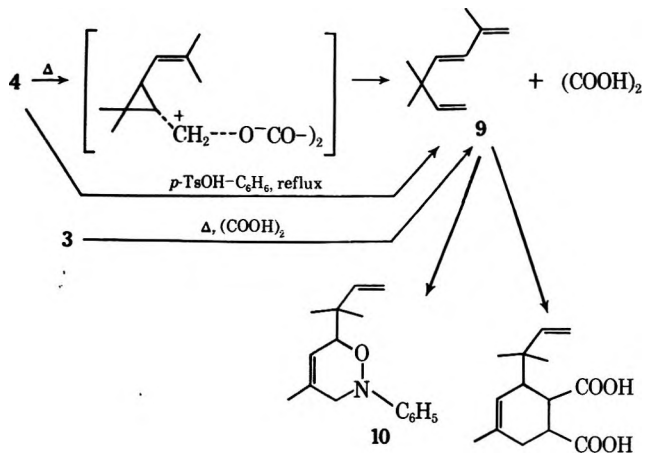


TABLE I

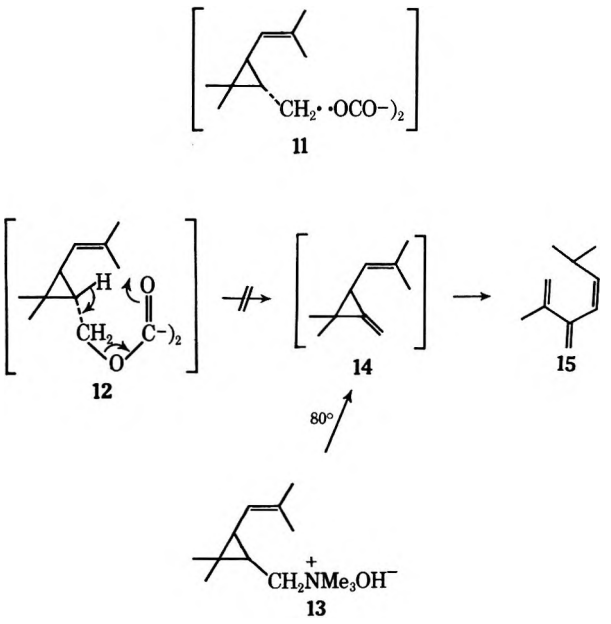
THERMAL DECOMPOSITION OF *trans*-CHRYSANTHEMYL OXALATE (4)

State	Addenda	Dec temp, °C	Yield of 9,[a] %
Neat	None	160	44
Neat	None	134 (100 mm)	51
Neat	Hydroquinone[b]	160	48
Solution	Quinoline	185	18

[a] Oxalic acid is also produced (see Experimental Section). [b] An equimolar amount was used.

been reported to give 2,6-dimethyl-3-methyleneheptа-1,4-diene (**15**) as a major product *via* a methylene cyclopropane derivative (**14**).[14] From this fact, the possibility of a concerted mechanism for the thermolysis of **4** could be excluded (Scheme II).[15] The presence of

SCHEME II



hydroquinone did not affect the decomposition (Table I). From this fact, the radical mechanism involving an intermediate such as **11** is disfavored and the ion-pair mechanism (Scheme I) is suggested. Furthermore, **9** was also produced by *p*-toluenesulfonic acid catalyzed decomposition of **4** in benzene and dehydration of **3** in the presence of oxalic acid, both of which can be assumed to proceed *via* an ion-pair or carbonium ion mechanism. The ion-pair mechanism, therefore, is the most plausible for the decomposition of **4**. The catalytic action of the primarily produced oxalic acid may be involved since the decomposition in quinoline lowered the yield of **9**. The decomposition under reduced pressure gave a somewhat better yield of **9**, which is explained by the lesser loss of **9** due to polymerization. In fact, considerable amounts of polymeric materials were produced in every run.

The decomposition temperature of **4** was considerably lower than those reported for oxalates of other primary and secondary alcohols; for example, cyclopentylcarbinyl and cyclohexyl oxalates have been reported to decompose at 360–370 and 250°, respectively.[16] This demonstrates clearly that the chrysanthemyl moiety has a stabilizing effect on the carbinyl cation involved at the ion-pair transition state by electronic and steric factors such as a strain relief *via* the cyclopropane ring opening, though the facility of thermal decomposition of a simple cyclopropylcarbinyl oxalate is not known yet.

Deamination Reaction of 7 and 18.—Chrysanthemylamines **7** and **18** were prepared by $LiAlH_4$ reduction of the corresponding amides obtained from *trans*- (**1**) and *cis*-chrysanthemic acids *via* the acid chlorides. The deamination was achieved *via* the diazotization of **7** and **18** with isoamyl nitrite–acetic acid in benzene.[17] The product from **7** was purified by chromatography on alumina to give a hydrocarbon (13%) and a mixture of acetates (44%). The hydrocarbon was characterized as **9**. The glpc of the acetate mixture exhibited three peaks in a 48:44:8 ratio. The two major components were isolated as colorless oils by preparative glpc and were characterized as artemisia acetate (**16**) (3,3,6-trimethyl-4-acetoxyhepta-1,5-diene) and *trans*-chrysanthemyl acetate (**8**), respectively. The spectral data of **16** were compatible with the assigned structure and, furthermore, the ir spectrum was practically superimposable on that reported for artemisia acetate from a natural source (*Artemisia annua L.*).[18] The characterization of **8** was based on spectral and glpc comparison with an authentic specimen.[19] The deamination of *cis*-amine **18** under the same conditions yielded also **9**, **16**, and *cis*-chrysanthemyl acetate (**19**) (Scheme III). The product distribution is summarized in comparison with those reported for deamination of cyclopropylcarbinylamine (**20**)[20] and for acetolysis of *trans*-chrysanthemyl tosylate (**17**)[19] (Table II).

The fact that only **16** and **9** were produced as the ring-opened products indicates selective ring cleavage at C_1–C_3 and demonstrates that an isobutenyl group possesses a larger stabilizing effect on the positive car-

(14) H. D. Roth, Abstracts of Papers, 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, PETR 2.

(15) Pyrolysis of trans acetate **8** resulted in polymerization accompanied with formation of small amounts of acetic acid.

(16) G. J. Karabatsos and K. L. Krumel, *J. Amer. Chem. Soc.*, **91**, 3324 (1969).

(17) *Cf.* L. Friedman and J. H. Bayless, *ibid.*, **91**, 1790 (1969).

(18) T. Takemoto and T. Nakajima, *Yakugaku Zasshi*, **77**, 1307 (1957); *Chem. Abstr.*, **52**, 4478e (1958).

(19) R. B. Bates and D. Feld, *Tetrahedron Lett.*, 4875 (1967).

(20) J. Bayless, L. Friedman, J. A. Smith, F. B. Cook, and H. Shechter, *J. Amer. Chem. Soc.*, **87**, 661 (1965).

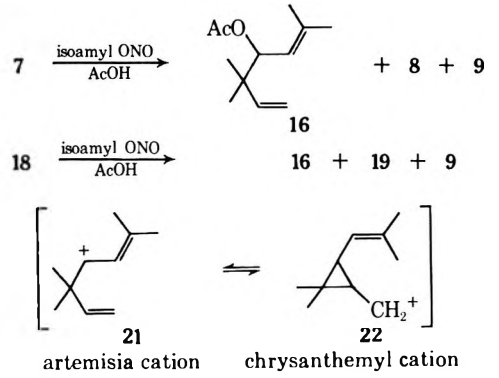
TABLE II

PRODUCT DISTRIBUTION OF DEAMINATION OF CHRYSANTHEMYLAMINE (7 AND 18)

Compd	Solvent	Products (yield, %)[a]		
7[b,c]	C_6H_6	16 (27.3)	8 (29.8)	9 (38)
18[c]	C_6H_6	16 (23.4)	19 (25.0)	9 (48)
20[d,e]	$CHCl_3$	Allyl acetate (13)	Cyclopropyl carbinyl acetate (67)	Cyclobutyl acetate (20)
17[f]	KOAc–HOAc[g] (at 40–60°)		8 (major product)	
	(at 85–90°)			9 (quantitative)[h]

[a] Estimated from relative peak areas on glpc. [b] For isolation, see Experimental Section. [c] An unidentified acetate was also produced both from 7 and 18 in 5 and 4.5%, respectively. [d] Taken from ref 20. [e] The principal product is bicyclo[1.1.0]butane (47%) which is not involved in the per cent composition in this table. [f] Taken from ref 19. [g] Acetolysis. [h] Isolated as the corresponding dimer.

SCHEME III



binyl carbon than a *gem*-dimethyl group.[19,21] However, the properties of the cationic species should be quite different from that involved in the acetolysis of **17** as demonstrated by the data in Table II.[22] The cationic species generated in the deamination is considered to be reactive[22] enough to be trapped by acetate anion rapidly before complete proton loss, affording **16** and **8** as the products corresponding to artemisia cation **21** and chrysanthemyl cation **22**. In the acetolysis at 85–90°, the intermediate cationic species is not highly reactive and consequently liberates a proton to afford the triene **9** as the major product. The formation of the acetate **8** at 40–60° could also be explained by an SN2 type reaction.[23] Comparison of the present data with those reported for **20** under similar conditions discloses that a larger ratio of ring-opened acetates to ring-retained ones is observed for **7** and **18** than for **20**, and, also, no insertion product is formed for **7** and **18** in contrast with the formation of bicyclobutane as one of the principal products for **20**. These differences may originate from the stabilizing effect of the isobutenyl group on the cationic species with a high energy. The fact that **7** and **18** gave the similar results could be explained reasonably by postulating a common intermediate such as a classical carbinyl and a homoallylic type cation but not by a bisected type one.[6]

Finally, it might be mentioned that the formation of **16** from **7** and **18** is useful for the synthesis of artemisia terpenes.

(21) H. M. Walborsky and L. Plonsker, *J. Amer. Chem. Soc.*, **83**, 2138 (1961); A. F. Thomas, *Chem. Commun.*, 1054 (1970).

(22) For other systems, see (a) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957); (b) W. G. Dauben and J. L. Chitwood, *J. Amer. Chem. Soc.*, **92**, 1624 (1970); (c) D. E. Applequist, M. R. Johnston, and F. Fisher, *ibid.*, **92**, 4614 (1970); (d) W. Cocker, D. P. Hanna, and P. V. R. Shannon, *J. Chem. Soc. C*, 1302 (1969).

(23) *Cf.* P. v. R. Schleyer, J. L. Fry, L. K. M. Lam, and C. J. Lancelot, *J. Amer. Chem. Soc.*, **92**, 2542 (1970), and preceding papers.

Experimental Section[24]

Preparation of *trans*-Chrysanthemyl Oxalate (4).—To an ice-cooled solution of 10.3 g (0.067 mol) of *trans*-chrysanthemol (**3**) which was obtained as an oil, $n^{19.5}D$ 1.4758 (lit.[25] $n^{23.5}D$ 1.4670), from ethyl chrysanthemate (**2**) by $LiAlH_4$ reduction and 5.3 g (0.067 mol) of dry pyridine in 100 ml of dry ether was added a solution of 4.9 g (0.038 mol) of oxalyl chloride in 25 ml of dry ether with stirring during 1 hr. After the addition, the stirring was continued for a further 1 hr and the mixture was allowed to stand overnight at room temperature. The mixture was poured onto ice–water and extracted with ether (three 150-ml portions). The combined ether extracts were washed with water and dried (Na_2SO_4). Removal of the solvent gave an oily residue which was purified on an alumina (Wako, neutral, grade III) column eluting with benzene to afford 3.8 g (51%) of the oxalate **4** as a colorless oil: $n^{17}D$ 1.4833; ir (neat) 1765, 1740 (C=O), 1670 and 850 cm^{-1} (C=C); nmr (CCl_4) τ 5.05 (broad d, 1, J = 7.0 Hz, CH=C), 5.68 and 5.78 (AB portion of an ABX pattern m, each 1, J_{gem} = 12 Hz, J_{vic} = 7.0 and 8.0 Hz, $CHCH_2OCO$), 8.31 (s, 6, $C=C(CH_3)_2$), 8.66 (d, d, 1, J = 5.5 and 7.0 Hz, C_3 H, partly overlapped with the signal at τ 8.82), 8.82 and 8.91 (s, each 3, C_2 *gem*-dimethyl), 9.00–9.30 (m, 1, C_1 H); mass spectrum *m/e* (rel intensity) 362 (M^+, 5), 226 (30), 136 (90), 121 (100).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.98; H, 9.35.

Thermal Decomposition of 4.—In a 10-ml, round-bottom flask fitted with a distillation head which is connected to a trap cooled with an ice–salt bath, 0.18 g (0.50 mmol) of **4** was heated under nitrogen in an oil bath. The oxalate decomposed at 160° to afford an oily product (0.060 g, 44%) collected at the trap. Its ir, nmr, and mass spectra were all superimposable on those of an authentic specimen of artemisia triene (**9**).[9] Oxalic acid was also obtained in 30–90° yield as a colorless solid which sublimed onto the wall of the flask and the distillation head.

The decomposition of **4** in the presence of an equimolar amount of hydroquinone was carried out similarly and that in quinoline was carried out by heating a solution of 0.30 g of **4** in 1 ml of dry quinoline at 185° (Table I).

Thermolysis of *trans*-Chrysanthemol (3) in the Presence of Oxalic Acid.—A mixture of 0.77 g (5.0 mmol) of **3** and 1.0 g (7.7 mmol) of oxalic acid dihydrate was heated as described above at 180° to afford 0.63 g (91%) of **9**.

Diels–Alder Reaction of 9. A. With Maleic Anhydride.—A mixture of 0.56 g (4.1 mmol) of **9** and 0.39 g (4.0 mmol) of maleic anhydride in 5 ml of dry benzene was heated under reflux for 1 hr. The cooled reaction mixture was stirred with 30 ml of 10% aqueous sodium hydroxide for 1 day at room temperature and the aqueous layer was separated which on neutralization with 10% hydrochloric acid gave 0.90 g of solids. Recrystallization from acetone afforded 0.66 g (64%) of colorless needles, mp 196–199° dec (lit.[10] mp 201–202°).

B. With Nitrosobenzene.—A mixture of 1.0 g (7.4 mmol) of **9** and 0.80 g (7.5 mmol) of nitrosobenzene in 50 ml of benzene

(24) All melting points and boiling points are uncorrected. Nmr spectra were recorded on a JEOL JNM-C-60HL spectrometer at 60 MHz with TMS an internal standard and mass spectra on a JEOL JMS-01SG mass spectrometer at 75 eV. Ir spectra are obtained with a JASCO IR-S infrared spectrophotometer. Glpc analyses were performed on a K-23 Hitachi gas chromatograph and preparative glpc on a Perkin-Elmer F-21 preparative gas chromatograph. Microanalyses were carried out with a Perkin-Elmer 240 elemental analyzer.

(25) M. Matsui, K. Yamashita, M. Miyano, S. Kitamura, Y. Suzuki, and M. Hamuro, *Bull. Agr. Chem. Soc. Jap.*, **20**, 89 (1956).

was stirred at room temperature for 1 day. Removal of the solvent gave a brownish oily residue which was purified on a silica gel column eluting with *n*-hexane–benzene (1:1 v/v). The main fraction (1.3 g) was further purified on an alumina column eluting with *n*-hexane to give 0.75 g (42%) of the adduct **10** as a colorless oil: ir (neat) 1600, 1500 and 760 (phenyl), 1640, 995 and 915 cm^{-1} (vinyl); nmr (CCl_4) τ 2.93 (m, 5, C_6H_5), 3.85–4.35 and 4.80–5.20 (a typical ABC pattern m, each 1 and 2, $CH=CH_2$), 4.46 (broad s, 1, C_5 H), 5.75 (broad s, 1, CHO), 6.44 (broad s, 2, CH_2N),[26] 8.22 (s, 3, $C=CCH_3$), 8.86 and 8.93 (s, each 3, $C(CH_3)_2$); mass spectrum *m/e* (rel intensity) 243 (M^+, 15), 131 (90), 105 (95), 94 (90), 92 (85), 80 (90), 78 (100).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.78; H, 8.60; N, 5.78.

Preparation of *trans*- (7) and *cis*-Chrysanthemylamines (18).—A solution of 9.0 g (0.054 mol) of *trans*-chrysanthemamide (**6**)[27] in 50 ml of dry ether was added to a suspension of 4.5 g (0.12 mol) of $LiAlH_4$ in 50 ml of dry ether under ice–water cooling and the resulting mixture was refluxed for 12 hr. Work-up in the usual way gave crude amine as an oil which was distilled to afford 6.0 g (81%) of the *trans*-amine **7** as a colorless oil: bp 87–90° (20 mm); $n^{17}D$ 1.4814; ir (neat) 3380, 3300, and 1595 (NH_2), and 845 cm^{-1} (CH=C); nmr (CCl_4) τ 5.18 (broad d, 1, J = 8.0 Hz, CH=C), 7.31 and 7.34 (each d, J = 7.0 Hz, CH_2N), 8.31 (s, 6, $C=C(CH_3)_2$), 8.88 (s, 2, NH_2, disappeared on deuteration), 8.88 and 8.97 (s, each 3, C_2 *gem*-dimethyl), 8.97 (d, d, 1, J = 5.0 and *ca.* 8.0 Hz, C_3 H, overlapped with the signal at 8.97), 9.45 (d, t, 1, J = 5.5 and 7.0 Hz, C_1 H).

Treatment of **7** with perchloric acid gave a crystalline perchlorate: mp 76–79°; ir (KBr) 3000 (NH_3^+), 1145, 1115, and 1090 (ClO_4^-), 845 cm^{-1} (CH=C).

Anal. Calcd for $C_{10}H_{20}O_4NCl$: C, 47.37; H, 7.98; N, 5.52. Found: C, 47.37; H, 7.75; N, 5.80.

Similarly *cis*-chrysanthemylamine (**18**) was obtained from *cis*-chrysanthemamide[27] in 54% yield as a colorless oil: bp 81–82° (15 mm); $n^{22}D$ 1.4767; ir (neat) 3335, 3280, and 1595 (NH_2), 845 cm^{-1} (CH=C); nmr ($CDCl_3$) τ 5.06 (broad d, 1, J = 8.0 Hz, CH=C), 7.00–7.60 (m, 2, CH_2N), 8.30 (s, 6, $C=C(CH_3)_2$), 8.45 (s, 2, NH_2, disappeared on deuteration), 8.70 (d, d, 1, J = 9.0 and 8.0 Hz, C_3 H), 8.87 and 8.99 (s, each 3, C_2 *gem*-dimethyl), 9.00–9.60 (m, 1, C_1 H). **18** gave a crystalline phenyl urea derivative: mp 96–98°; ir (KBr) 3320, 1645, and 1560 (NHCONH), 1595, 1500, and 765 (phenyl), 840 cm^{-1} (CH=C).

Anal. Calcd for $C_{17}H_{24}ON_2$: C, 74.96; H, 8.88; N, 10.29. Found: C, 75.15; H, 9.12; N, 10.56.

Deamination of Chrysanthemylamines (7 and 18).—A solution of 1.53 g (10 mmol) of **7**, 1.29 g (11 mmol) of isoamyl nitrite, and 0.60 g (10 mmol) of acetic acid in 20 ml of benzene was heated under reflux for 5 hr. Removal of the solvent gave an oily residue which was analyzed on glpc (Table II) and then purified by chromatography on an alumina (Wako, neutral, grade II) column. The first fraction eluted with *n*-hexane afforded 0.175 g (13%) of **9** as an oil identified by comparison with an authentic sample. The second fraction eluted with benzene gave 0.86 g (44%) of the acetate mixture which was analyzed on glpc to give three peaks in a 48:44:8 ratio. Separation by preparative glpc by using a 1.8 m × 8 mm U-shaped column packed with 10% silicone SE-30 on 60–80 mesh Chromosorb W, at 150° gave two pure acetates, **16** and **8**. One of the acetates was artemisia acetate: ir (neat) 1730 (OAc), 1645, 980 and 920 (vinyl), 1675 and 845 cm^{-1} (isobutenyl);[18] nmr (CCl_4) τ 3.94–4.40 and 4.70–5.28 (a typical ABC pattern m, 3, $CH=CH_2$), 4.77 (d, 1, J = 10 Hz, C=CH), 5.01 (d, 1, J = 10 Hz, CHOAc), 8.08 (s, 3, OAc), 8.28 (s, 6, $C=C(CH_3)_2$), 9.04 (s, 6, $C(CH_3)_2$); mass spectrum *m/e* (rel intensity) 196 (M^+, 15), 124 (70), 110 (100), 108 (95).

Another acetate was identified as *trans*-chrysanthemyl acetate (**8**) by comparison (ir and glpc) with an authentic sample.

The third fraction eluted with benzene gave 0.17 g (12% recovery) of the recovered amine **7**.

Deamination of the *cis*-amine **18** was carried out similarly and the products were analyzed on glpc (Table II).

Preparation of *trans*- (8) and *cis*-Chrysanthemyl Acetates (19).—Since the details about chrysanthemyl acetates (**8** and **19**) have not been described in literature,[19] **8** and **19** were prepared from the corresponding *trans*- (**3**) and *cis*-chrysanthemols, respectively, by acetylation with acetic anhydride in pyridine.

8 was obtained as a colorless oil in 81% yield: bp 113–114° (21 mm); $n^{17}D$ 1.4612; ir (neat) 1740 (C=O), 1665 and 845 cm^{-1} (CH=C); nmr (CCl_4) τ 5.15 (broad d, 1, J = 7.5 Hz, CH=C), 5.81 and 6.11 (AB portion of an ABX pattern m, each 1, J_{gem} = 13.0 Hz and J_{vic} = 7.0 and 9.0 Hz, a diastereotopic CH_2OAc), 8.03 (s, 3, $OCOCH_3$), 8.33 (s, 6, $C=C(CH_3)_2$), 8.63 (d, d, 1, C_3 H), 8.88 and 8.96 (s, each 3, C_2 *gem*-dimethyl), 9.10–9.60 (m, 1, C_1 H).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.43; H, 10.26.

19 was obtained as a colorless oil in 56% yield: bp 105.5–106.5° (21 mm); $n^{18}D$ 1.4633; ir (neat) 1735 (C=O), 1655 and 840 cm^{-1} (CH=C); nmr (CCl_4) τ 5.15 (broad d, 1, J = 8.0 Hz, CH=C), 6.05 (d, 2, J = 7.5 Hz, CH_2OAc), 8.05 (s, 3, $OCOCH_3$), 8.31 (s, 6, $C=C(CH_3)_2$), 8.67 (t, 1, J = 8.0 Hz, C_3 H), 8.86 and 9.00 (s, each 3, C_2 *gem*-dimethyl), 8.90–9.20 (m, 1, C_1 H).

Registry No.—**4**, 29172-38-1; **7**, 29172-39-2; **7** perchlorate, 29172-40-5; **8**, 29172-41-6; **10**, 29182-49-8; **16**, 29182-50-1; **18**, 29172-42-7; **18** phenylurea derivative, 29172-43-8; **19**, 29172-44-9.

(26) *Cf.* T. Sasaki, S. Eguchi, T. Ishii, and H. Yamada, *J. Org. Chem.*, **35**, 4273 (1970), and references cited therein.

(27) T. Sasaki, S. Eguchi, and M. Ohno, *Tetrahedron*, **25**, 2145 (1969).

Tumor Inhibitors. LXII.[1] The Structures of Acerotin and Acerocin, Novel Triterpene Ester Aglycones from the Tumor Inhibitory Saponins of *Acer negundo*[2]

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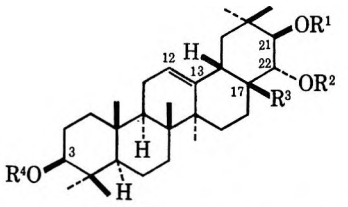
The aglycones acerotin (**1**) and acerocin (**2**) have been characterized as the major aglycones of the tumor inhibitory saponin P isolated from *Acer negundo* L. The two aglycones are diesters of the new acidic triterpene acerogenic acid (**3**). The structure of **3** was determined from its spectral properties and by chemical studies including conversion into 16-deoxybarringtogenol C. The ester groups were characterized as acetate and the novel nonadienoates corresponding to **11** and **12**, present in **1** and **2**, respectively. 24-Hydroxyacerogenic acid (**18**) has been characterized as one of the major sapogenins derived from the tumor inhibitory saponin Q. Hydrolysis of saponin Q also yielded acids **11** and **12**. The potential significance of the unsaturated ester functions for the growth inhibitory activity of the *Acer* saponins is discussed.

In the course of a continuing search for tumor inhibitors of plant origin, an ethanolic extract of the leaves and stems of *Acer negundo* L. (*Aceraceae*) has been shown to possess significant inhibitory activity. Systematic fractionation led to the isolation of the active principles as the chromatographically homogeneous acids, saponin P and saponin Q.[4] Saponin P was active against the sarcoma 180 and Walker intramuscular carcinosarcoma 256 tumor systems,[4] and on further testing the high therapeutic index in the latter system indicated "activity sufficient for recommendation as a clinical candidate."[5] The National Cancer Institute has since procreud a large collection of *Acer negundo* for extraction of *Acer* saponin P in a quantity sufficient for preclinical toxicological studies and preliminary clinical trials. The structural elucidation of the aglycones acerotin (**1**) and acerocin (**2**) formed by hydrolysis of saponin P have been briefly reported,[6] and we describe herein our detailed structural studies.

Acid hydrolysis of saponin P yielded glucose and arabinose, which were identified by vapor phase chromatography of their trimethylsilyl ethers, and a mixture of acidic aglycones. The aglycones showed only one major spot on examination by tlc on silica gel but on alumina showed two slightly separated major components. Fractionation first by tlc on silica gel and then repeatedly on alumina yielded the major components acerotin (**1**, R_f 0.57) and acerocin (**2**, R_f 0.55).

Elemental analysis and high-resolution mass spectrometry showed **1** and **2** to be isomeric $C_{41}H_{62}O_7$ compounds. The ultraviolet spectra (**1**, λ_{max} 264 mμ, and **2**, λ_{max} 266 mμ) were very similar, and the infrared spectra of both compounds contained bands assignable to a hydroxyl, a saturated ester, an unsaturated ester, a carboxyl, and a double bond (*i.e.*, **1**, 2.81, 2.94, 3.14, 5.73, 5.76, 5.87, 6.11, and 6.20 μ, respectively). The nmr spectra of **1** and **2** were very similar in the high field region and both contained an acetyl group signal at τ 8.06. Although both spectra contained an AB



R_{tt} = -CO(CH=CH)$_2$CH(CH$_3$)CH$_2$CH$_3$ (*t*)

R_{ct} = -CO(CH=CH)(CH=CH)CH(CH$_3$)CH$_2$CH$_3$ (*c*, *t*)

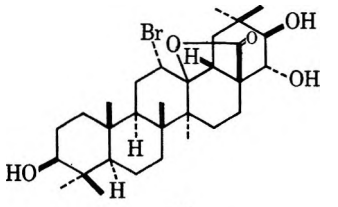
1, $R^1 = R_{tt}$; R^2 = Ac; $R^3 = CO_2H$; R^4 = H
2, $R^1 = R_{ct}$; R^2 = Ac; $R^3 = CO_2H$; R^4 = H
3, $R^1 = R^2 = R^4$ = H; $R^3 = CO_2H$
4, $R^1 = R^2 = R^4$ = Ac; $R^3 = CO_2H$
5, $R^1 = R^2 = R^4$ = H; $R^3 = CO_2CH_3$
6, $R^1 = R^2 = R^4$ = Ac; $R^3 = CO_2CH_3$
7, $R^1 = R^2 = R^4$ = H; $R^3 = CH_2OH$
8, $R^1 = R_{tt}$; $R^2 = R^4$ = H; $R^3 = CO_2H$
9, $R^1 = R_{ct}$; $R^2 = R^4$ = H; $R^3 = CO_2H$
10, $R^1 = R_{tt}$; $R^2 = R^4$ = Ac; $R^3 = CO_2H$

$CH_3O_2C(CH=CH)(CH=CH)CH(CH_3)CH_2CH_3$ (*t*, *t*)

11

$CH_3O_2C(CH=CH)(CH=CH)CH(CH_3)CH_2CH_3$ (*c*, *t*)

12



13

quartet (τ 4.65 and 4.98, J = 10 Hz), there were marked differences in the τ 2–5 region. The mass spectra of the aglycones were virtually identical and both contained a base peak at m/e 137 and a strong peak at m/e 109, suggesting that a large ester grouping was being lost.

Alkaline hydrolysis of **1** and **2** yielded different unsaturated C_9 acids but the same acidic triterpene, acerogenic acid (**3**). Acerogenic acid, $C_{30}H_{48}O_5$, lacked the ultraviolet absorption and the mass spectral peaks at m/e 137 or 109 present in the spectra of the aglycones.

(1) Part LXI: T. Kurokawa, K. Nakanishi, W. Wu, H. Y. Hsu, M. Maruyama, and S. M. Kupchan, *Tetrahedron Lett.*, 2863 (1970).

(2) Supported by grants from the National Cancer Institute (CA-04500 and CA-11718) and the American Cancer Society (T-275).

(3) Author to whom inquiries should be directed at the University of Virginia.

(4) S. M. Kupchan, R. J. Hemingway, J. R. Knox, S. J. Barboutis, D. Werner, and M. A. Barboutis, *J. Pharm. Sci.*, **56**, 603 (1967).

(5) J. M. Venditti and B. J. Abbott, *Lloydia*, **30**, 232 (1967).

(6) S. M. Kupchan, M. Takasugi, R. M. Smith, and P. Steyn, *Chem. Commun.*, 969 (1970).

The infrared spectra contained bands at 2.92 (OH) and 5.90 μ (carboxyl); the carboxylate salt showed bands at 6.38 and 7.20 μ. The nmr spectrum (pyridine-d_5) contained signals for three protons on carbon carrying hydroxyl (τ 5.6–6.3, m).

On acetylation **3** yielded a triacetate **4**, $C_{36}H_{54}O_8$, whose nmr spectrum contained signals assignable to acetyl groups at τ 7.96, 7.99, and 8.01 and to protons on carbon carrying acetoxyl at τ 4.70 and 5.06 (AB quartet, J = 11 Hz) and τ 5.51 (bt, J = 8 Hz). On treatment with diazomethane, **3** gave a methyl ester **5**, $C_{31}H_{50}O_5$, ir (KBr) 5.82 μ, whose nmr spectrum contained a signal at τ 6.25 (OMe). Acetylation of **5** yielded the triacetyl methyl ester **6**, $C_{37}H_{56}O_8$. The infrared spectrum of **6** lacked hydroxyl bands but contained bands at 5.69, 5.77 (ester), and 8.04 μ (acetate), and the nmr spectrum contained signals at τ 4.81 and 5.04 (AB quartet, J = 10 Hz) and τ 5.51 (dd, J = 6,9 Hz) corresponding to protons on carbon carrying acetoxyl, as well as signals for seven quaternary methyl groups, τ 8.84, 8.92, 9.07, 9.10, 9.13 (6 H), and 9.31, and one olefinic proton, τ 4.65 (bt, J = 7 Hz). Therefore, the oxygen atoms in **3** could be assigned to three secondary hydroxyl groups and a carboxyl group.

From the molecular formula and number of *C*-methyl groups present, **3** was proposed to have a β-amyrin skeleton containing a 12,13 double bond. The carboxyl group could be assigned to C-17, as on treatment of **3** with bromine in methanol[7] it formed the bromo-γ-lactone **13**, $C_{30}H_{47}BrO_5$. The infrared spectrum of **13** contained a band at 5.66 μ (γ-lactone) and the nmr spectrum lacked a signal assignable to an olefinic proton. The circular dichroism of acerogenic acid, λ 225 mμ ($\Delta\epsilon$ − 1.6), was found to be very similar to that reported for a series of Δ^{12}-triterpene-28-carboxylic acids,[8] indicative that it had a similar conformation.

These assignments were confirmed by the mass spectra of **3** and **5**, which exhibited a typical retro-Diels–Alder fragmentation of the C ring characteristic of the $\Delta^{12,13}$-β-amyrin skeleton.[9] Strong peaks were present at *m/e* 280, 262 (−18), 244 (−36), and 234 (−46) from **3**, and *m/e* 294, 276 (−18), 258 (−36), and 234 (−60) from **5**, demonstrating the presence of the carboxyl group and two hydroxyl groups in the D,E ring system. Significant peaks in both spectra at *m/e* 207 and 190 (−17) could be attributed to the A,B ring system carrying one hydroxyl group. On biogenetic grounds this hydroxyl was assigned to C-3 and the signal at τ 5.51 (dd, J = 6, 9 Hz) in the spectrum of **6** could be assigned to the C-3 proton. In the mass spectra of the triacetates **4** and **6** corresponding peaks appeared, with the appropriate fragmentations at *m/e* 364 and 378, respectively, for the D,E ring system and at *m/e* 190 (−60) for the A,B ring system.

From the nmr spectra the hydroxyl groups in the D,E ring system could be formulated as a diequatorial diol, as the coupling (J = 10 Hz) between the protons on carbon carrying oxygen suggested a diaxial relationship. If the D,E ring system is cis-fused and ring E is in a chair conformation, the diol could be located only at C-15,16 or C-21,22. C-15 α- and β-hydroxyl groups in derivatives of dumortierigenin[10] and the C-15 hydroxyl group in the 15α,16α-*cis*-diolentagenic acid[11] have been found to be acetylated only under conditions considerably more vigorous than those used to prepare **6**. Thus, the diol was tentatively assigned to C-21,22, and the novel structure **3** was proposed for the genin.

Confirmation of the oxygenation pattern and proposed stereochemistry was obtained by reduction of **5** with lithium aluminum hydride to yield the tetrol **7**, identical by direct comparison with 16-deoxybarringtogenol C.[12] The structure of 16-deoxybarringtogenol C has been determined by interrelation[13] with barringtogenol C, defined by X-ray crystallography of its diester.[14] Acetylation of **7** gave a tetraacetate, whose physical properties corresponded to those reported.[13]

The unsaturated acids formed on hydrolysis of the aglycones were first separated by tlc on silica gel and were then methylated by treatment with diazomethane. The methyl esters were purified by vapor phase chromatography and were collected as $CDCl_3$ solutions. Acerotin (**1**) yielded the optically active 2,4-*trans*-diene ester **11**. The ultraviolet spectrum, λ_{max} 260 mμ, and the infrared spectrum, 5.87, 6.10, 6.19, 10.00 μ (trans olefin), were very similar to those of methyl 2,4-*trans*-decanedienoate.[15] The nmr spectrum contained signals assignable to a *sec*-butyl group [τ 9.12 (t, J = 7 Hz, 3 H), 8.96 (d, J = 7 Hz, 3 H), 8.59 (quintet, J = 7 Hz, 2 H), and 7.81 (septet, J = 7 Hz, 1 H)], a methoxyl group [τ 6.28 (s, 3 H)], and four olefinic protons [τ 4.20 (d, J = 15.5 Hz, α H), 3.90–3.85 (m, γ and δ H), and 2.73 (dd, J = 15, 10 Hz, β H)]. The chemical shift and observable couplings of the olefinic protons agreed well with those reported for methyl 2,4-*trans*-sorbate [τ 4.32 (α H), 3.96 (γ H), 3.85 (δ H), 2.83 (β H), $J_{\alpha,\beta}$ = 15.8, $J_{\beta,\gamma}$ = 10.5 Hz][16] and differed from those reported for a 2-*trans*-4-*cis*-diene amide.[17] The mass spectrum contained a molecular ion (*m/e* 168) and strong peaks corresponding to loss of C_2H_5 (*m/e* 139) and C_4H_9 (*m/e* 111), whereas only small peaks were present for loss of CH_3 (*m/e* 153) and C_3H_7 (*m/e* 125), as expected for a compound containing a *sec*-butyl group.[18] The peak at *m/e* 111 is characteristic of an α,β : γ,δ-diene ester and can be represented as a pyrylium ion.[19]

Acerocin (**2**) yielded the isomeric optically active 2-*cis*-4-*trans*-diene ester **12**. The ultraviolet spectrum, λ_{max} 263 mμ, and infrared spectrum, λ_{max} 5.87, 6.13, 6.26, 10.10 (trans olefin), and 10.42 μ (cis olefin), were comparable to those of methyl 2-*cis*-4-*trans*-decadienoate.[15] The nmr spectrum contained signals for a *sec*-butyl group [τ 9.10 (t, J = 7 Hz, 3 H), 8.91 (d, J = 7 Hz, 3 H), 8.59 (quintet, J = 7 Hz, 2 H), 7.76 (septet, J = 7 Hz)], a methoxyl group [τ 6.26 (s, 3 H)], and four olefinic protons [τ 4.45 (d, J = 11 Hz, α H), 4.05

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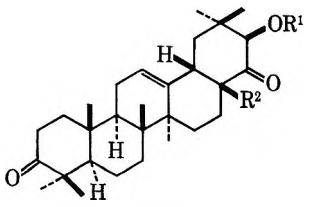
(dd, J = 8, 16 Hz, δ H), 3.45 (t, J = 11.5 Hz, β H), 2.65 (dd, J = 11.5, 16 Hz, γ H)]. The olefinic couplings were confirmed by double irradiation and the chemical shifts and the couplings of the olefinic protons were comparable to the signals from the methyl 2-*cis*-4-*trans*-sorbate[16] [τ 4.52 (α H), 4.01 (δ H), 3.53 (β H), and 2.61 (γ H), $J_{\alpha,\beta}$ = 11.6, $J_{\beta,\gamma}$ = 11.5, $J_{\gamma,\delta}$ = 15.7, and $J_{\delta,\epsilon}$ = 7.05 Hz].

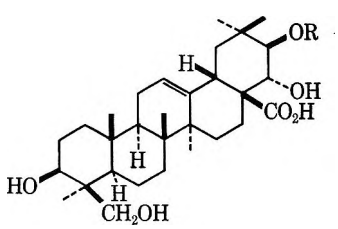
The differences in the olefinic proton signals of the two ester functions were clearly responsible for the differences between the nmr spectra of **1** and **2** and the presence of the corresponding olefin proton signals in the spectra of the aglycones confirmed that no isomerization of the esters had occurred on hydrolysis.[15] The formation of the same fragmentation ions in the mass spectra of the isomeric aglycones showed that the two ester functions also are isomeric.

As in the nmr spectra of the aglycones the AB quartet appeared at low field; the ester groupings were assigned to C-21 and C-22. Consequently, in saponin P the sugar moiety is located at C-3. In order to determine the relative orientation of the ester functions, partial acid hydrolysis of **1** and **2** was carried out to give the respective deacetyl derivative **8** and **9**. With alkali, only **3** could be isolated in good yield, as the intermediates were themselves rapidly hydrolyzed. The ultraviolet spectrum of **8** showed that it still contained the diene ester group but its nmr spectrum lacked signals for an acetyl group and the C-21,22 protons now appeared at τ 5.13 and 6.12 (AB quartet, J = 11 Hz). Acetylation of **8** yielded acetylacerotin (**10**), demonstrating that ester exchange had not occurred between C-21 and C-22. On tlc plates **9** absorbed ultraviolet light and thus also contained an unsaturated chromophore.

Jones oxidation of **8** and **9** afforded the corresponding diketo acids **14** and **15**, which on heating briefly were decarboxylated to yield the diketones **16** and **17**, respectively. The diketones were characterized by their mass spectra, which contained strong ions at m/e 137 and 109. Their ultraviolet spectra confirmed that they still contained the diene chromophore. Thus the acetoxyl group was located at C-22, β to the carboxyl



14, $R^1 = R_{tt}$; $R^2 = CO_2H$
15, $R^1 = R_{ct}$; $R^2 = CO_2H$
16, $R^1 = R_{tt}$; $R^2 = H$
17, $R^1 = R_{ct}$; $R^2 = H$



18, R = H
19, R = R_{ct}

group, and the diene ester could be assigned to C-21, giving the complete structure of the aglycones as **1** and **2**.

Acidic hydrolysis of the second tumor inhibitor, saponin Q, gave a complex mixture of aglycones, which was fractionated by tlc. Most of the fractions were still mixtures but one major fraction, aglycone B, was homogeneous and was studied further. The molecular ion in the mass spectrum corresponded to $C_{39}H_{60}O_7$ (m/e 640). The ultraviolet spectrum, λ_{max} 262 mμ, suggested the presence of a diene ester group and the mass spectrum contained ions at m/e 137 and 109 characteristic of a C_9-diene ester function. Signals in the nmr spectrum at τ 4.20 (d, J = 11 Hz, α H) and 3.39 (t, J = 11 Hz, β H) were comparable to those in the spectrum of **2** and suggested the probable presence of a 2-cis-4-trans acyl group. There was no signal attributable to an acetyl group.

Alkaline hydrolysis of aglycone B yielded an acidic sapogenin, $C_{30}H_{48}O_6$, which was also isolated from the products of successive acidic and alkaline hydrolysis of saponin Q. Elemental analysis and mass spectroscopy showed the presence of an additional oxygen compared to acerogenic acid. Methylation using ethereal diazomethane gave a methyl ester, $C_{31}H_{50}O_6$. On acetylation the methyl ester yielded a methyl ester tetraacetate, $C_{39}H_{58}O_{10}$, and thus the additional oxygen could be assigned to a fourth hydroxyl group.

The mass spectra of these three compounds were studied. Peaks at m/e 280, 294, and 378 in acid, ester, and peracetyl ester, respectively, could be assigned to the D,E ring system.[9] They appeared at the same mass and showed the same fragmentations as ions in the spectra of acerogenic acid, its methyl ester, and triacetyl methyl ester.

A smaller peak at m/e 224 in the spectrum of the methyl ester was assignable to the A,B ring system and appeared 17 mass units higher than in the spectrum of **5**. Thus the D,E ring system could be assumed to have the same substituents as acerogenic acid and the additional hydroxyl group could be assigned to the A,B ring system.

The nmr spectrum of the tetraacetyl methyl ester was very similar to the spectrum of **6**. It contained signals at τ 4.82 and 5.05 (AB quartet, J = 10.8 Hz) and at τ 5.43 (bt) assignable to a C-21,22 diacetate and a C-3 (CHOH) proton, respectively. In addition, it contained a second AB quartet (J = 11.5 Hz) at τ 5.65 and 5.89, which could be assigned to an axial $-CH_2OAc$ system at either C-24 or C-25.[20]

Treatment of the methyl ester with acetone and perchloric acid yielded an acetonide, $C_{34}H_{54}O_6$. Sapogenin B was therefore proposed to be 24-hydroxyacerogenic acid (**18**) and the aglycone B could be postulated to be the C-21 2-*cis*-4-*trans*-diene ester **19**. It is possible that in saponin Q the nucleus was acetylated at C-22, in a similar way to **1** and **2** and that **19** was an artefact formed by selective deacetylation under the acidic conditions of the aglycone formation reaction.

Direct alkaline hydrolysis of saponin P yielded after methylation the diene esters **11** and **12** in a 1:1.5 ratio, similar to the estimated ratio of **1** and **2** present in the

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acid hydrolysate. Hydrolysis of saponin Q, followed by methylation, also yielded the same diene esters as the main volatile components.

As the presence of α,β-unsaturated carbonyl functions has been shown to be responsible for the tumor inhibitory activity of other natural products,[21,22] the unsaturated esters in saponin P may make a highly significant contribution in making the compound the most promising of the known tumor-inhibitory saponins.[23]

Experimental Section

Infrared spectra were measured on a Beckman IR-9 or Perkin-Elmer 257 spectrometer and ultraviolet spectra were measured on a Coleman-Hitachi EPS-3T or Beckman DK-2A spectrometer in methanol solutions. CD spectra were measured using a modified JASCO spectrometer. Melting points were determined using a Thomas-Hoover melting point apparatus. Nmr spectra were recorded on a Varian A-60A or HA-100 instrument using TMS as reference as $CDCl_3$ solutions unless otherwise stated. Mass spectra were measured on an AEI MS902 high-resolution instrument or a Hitachi Perkin-Elmer RMU-6E low-resolution instrument. Vpc was carried out on a Varian Aerograph 1760 instrument using either (a) 8% QF1, 9 ft × 1/8 in. at 100° or (b) 10% Carbowax 20M, 6 ft × 1/8 in. at 100°, and the retention times are expressed relative to methyl decanoate (R_{t10}). Vpc of sugars was carried out on a F & M Model 700 chromatograph using a 10% SE-30 column at 160–240°. Tlc was carried out on precoated tlc plates of silica gel F-254 or aluminum oxide F-254 (E. Merck). Analyses were carried out by Spang microanalytical service, Ann Arbor, Mich.

Acerotin (1) and Acerocin (2).—A solution of saponin P (1.0 g) in EtOH (25 ml) and 2 *N* HCl (25 ml) was heated at 100° for 80 min. The mixture was extracted with chloroform (total 100 ml), which was washed with 75% aqueous EtOH, dried, and evaporated. The residue was separated by tlc on silica gel ($CHCl_3$–EtOH 10:1). The major band was extracted and separated by tlc on alumina (H_2O-saturated butanone).

After acidification the upper band was extracted with butanone to give a residual oil. Repeating the separation on silica gel and then on alumina yielded a gum, which on crystallization from aqueous EtOH yielded acerotin (1, 14 mg): R_f (alumina, H_2O–saturated butanone) 0.57; mp 240–243°; $[\alpha]^{24}D$ 67° (c 0.73, $CHCl_3$); uv max 264 mμ (ε 28,400); ir (KBr) 2.81, 2.94, 3.14, 5.73, 5.76, 5.87, 6.11, and 6.20 μ; mass spectrum *m/e* (rel intensity) 666 (M^-) (10), 466 (71), 452 (19), 407 (42), 398 (14), 368 (11), 304 (47), 276 (20), 244 (29), 216 (20), 207 (36), 199 (40), 190 (34), 137 (100), 109 (75).

Anal. Calcd for $C_{41}H_{62}O_7$: C, 73.83; H, 9.37; mol wt, 666.4496. Found: C, 73.63; H, 9.11; mol wt (mass spectrum), 666.4496.

The lower band was extracted and repurified as above to yield crystals (51 mg), which on crystallization twice from aqueous EtOH gave acerocin (2): R_f (alumina, H_2O–saturated butanone) 0.55; mp 205–207°; $[\alpha]^{24}D$ 104° (c 0.94, $CHCl_3$); uv max 266 mμ (ε 22,900); ir (KBr) 2.78, 2.92, 3.14, 5.71, 5.77, 5.81, 6.12, and 6.26 μ; mass spectrum *m/e* (rel intensity) 666 (19), 512 (11), 466 (87), 452 (20), 424 (17), 407 (38), 398 (10), 368 (18), 304 (48), 276 (19), 244 (27), 216 (13), 207 (43), 199 (33), 190 (37), 137 (100), 109 (94).

Anal. Calcd for $C_{41}H_{62}O_7$: C, 73.83; H, 9.37; mol wt, 666.4496. Found: C, 74.04; H, 9.46; mol wt (mass spectrum), 666.4513.

Sugars from Saponin P.—Saponin P was hydrolyzed as above but using 1 *N* HCl and the acidified aqueous solution was extracted with chloroform. The aqueous solution was evaporated and the residue, after trimethylsilylation[24] was examined by vpc. By comparison with standards, which had been treated under the same hydrolysis conditions, it was shown that saponin P had yielded arabinose and glucose in a 1:4 ratio.

Hydrolysis of Acerotin (1).—A solution of acerotin (10 mg) in 5% methanolic KOH (1 ml) was heated on a steam bath for 1 hr under nitrogen. The solution was concentrated, acidified, and extracted with hexane (two 2-ml portions) which was washed and evaporated to give an oil (2.0 mg). The oil was treated with ethereal diazomethane to give a solution which was separated by vpc (column a). The major component, which was trapped as a $CDCl_3$ solution, was the diene ester 11: R_{t10} (column a) 1.20; R_{t10} (column b) 1.49; CD λ_{max} 260 mμ (Δε 2.7) [assuming ε (uv) 28,500[15]]; uv max 260 mμ; ir ($CDCl_3$) 5.87, 6.10, 6.19, and 10.00 μ; mass spectrum (vpc inlet, column a) *m/e* 168 (M^+), 139, 111, 79.

The aqueous solutions were combined and extracted with $CHCl_3$–MeOH which was washed with aqueous MeOH and evaporated to give a solid. The solid was separated by tlc on silica gel (H_2O-saturated butanone) to give, after crystallization from aqueous MeOH, acerogenic acid (3, 6.7 mg): R_f 0.42; mp 308–310°; $[\alpha]^{24}D$ 66° (c 0.95, EtOH); CD λ 222 mμ (Δε −1.48); uv end absorption 210 mμ (ε 4400); ir (KBr) 2.92, 5.90 μ.

Anal. Calcd for $C_{30}H_{48}O_5$: C, 73.73; H, 9.90; mol wt, 488. Found: C, 73.87; H, 10.06; mol wt (mass spectrum), 488.

Hydrolysis of Acerocin (2).—Hydrolysis of acerocin (2, 10 mg) by the same method as 1 gave acerogenic acid (3, 7.1 mg), identical with 3 from 1 on comparison by melting point, mixture melting point, tlc, and ir and mass spectra, and the volatile diene ester 12 (as $CDCl_3$ solution): R_{t10} (column a) 0.57; R_{t10} (column b) 1.00; CD λ_{max} 263 mμ (Δε 1.5) [assuming ε (uv) 23,800[15]]; uv max 263 mμ; ir ($CDCl_3$) 5.87, 6.13, 6.26, 10.10, and 10.42 μ.

Bromo-γ-lactone 13.—A solution of 3 (26 mg) in methanol (2 ml) was treated with a solution of bromine (10 mg) in methanol (1 ml). After 10 min the solution was concentrated and cooled to give crystals (26 mg). Recrystallization from methanol gave the bromolactone 13: mp 240–241° dec; $[\alpha]^{24}D$ 69° (c 0.59, EtOH); ir (KBr) 5.66 μ.

Anal. Calcd for $C_{30}H_{47}BrO_5 \cdot H_2O$: C, 61.52; H, 8.43; Br, 13.64; mol wt, 567. Found: C, 61.31; H, 8.31; Br, 13.62; mol wt (mass spectrum), 568 and 566.

Triacetylacerogenic Acid (4).—A solution of acerogenic acid (25 mg) in acetic anhydride (0.25 ml) and pyridine (0.25 ml) was heated for 1 hr on a steam bath. Working up in the normal way gave the crude product which was separated by tlc on silica gel ($CHCl_3$–EtOH 10:1) to give a gum (27 mg). Crystallization from acetonitrile yielded 4 (17 mg): mp 296–297° dec; $[\alpha]^{24}D$ 60° (c 0.81, $CHCl_3$); ir (KBr) 5.71 and 5.87 μ.

Anal. Calcd for $C_{36}H_{54}O_8$: C, 70.33; H, 8.85; mol wt, 614. Found: C, 70.44; H, 8.81; mol wt (mass spectrum), 614.

Methyl Acerogenate (5).—A solution of acerogenic acid (3, 11 mg) in MeOH (2 ml) was treated with an excess of ethereal diazomethane. The solvent was evaporated and the residue separated by tlc on silica gel ($CHCl_3$–EtOH 10:3) to give a solid, which on recrystallization from methanol yielded 5 (10 mg): mp 236–238°; $[\alpha]^{24}D$ 67° (c 1.01, EtOH); ir (KBr) 5.82 μ.

Anal. Calcd for $C_{31}H_{50}O_5$: C, 74.06; H, 10.03; mol wt, 502. Found: C, 73.93; H, 9.96; mol wt (mass spectrum), 502.

Methyl Triacetylacerogenate (6).—A solution of 5 (31 mg) in acetic anhydride (0.5 ml) and pyridine (0.5 ml) was kept at room temperature for 24 hr. Working up the reaction yielded a resin (40 mg) which was crystallized from methanol to give 6 (24 mg): mp 212–213°; $[\alpha]^{24}D$ 54° (c 1.08, $CHCl_3$); ir (KBr) 5.69, 5.77, and 8.04 μ.

Anal. Calcd for $C_{37}H_{56}O_8$: C, 70.67; H, 8.98; mol wt, 628. Found: C, 70.78; H, 8.95; mol wt (mass spectrum), 568 ($M^+ - 60$).

Reduction of 5.—A solution of 5 (103 mg) in THF (20 ml) was refluxed with lithium aluminum hydride (250 mg) for 20 hr. Wet THF was added and the solution was filtered. The solid was acidified and extracted with $CHCl_3$–EtOH (10:1) and the combined organic solutions were evaporated. The residue was separated by tlc on silica gel ($CHCl_3$–EtOH 10:1) to give crystals (98 mg). Recrystallization from ethanol yielded the tetrol 7, mp 298–301°.

Anal. Calcd for $C_{30}H_{50}O_4$: C, 75.90; H, 10.62; mol wt, 474. Found: C, 76.01; H, 10.69; mol wt (mass spectrum), 474.

The product was identical with 16-deoxybarringtogenol C on the basis of direct comparison[12] by mixture melting point, mixture tlc, and mass and infrared spectra. (The ir spectral comparison was kindly carried out by Professor Yosioka.)

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Acetylation gave a tetraacetate: mp 223–224°; $[\alpha]^{24}D$ 55° (*c*, 1.10, $CHCl_3$); ir (KBr) 5.74 μ [lit.[13] mp 225–226°; $[\alpha]D$ 50° (*c* 0.8, $CHCl_3$)]. (Nmr spectra were found to be comparable by Professor Yosioka.)

Anal. Calcd for $C_{38}H_{58}O_8$: C, 70.99; H, 9.09; mol wt, 642. Found: C, 70.99; H, 9.11; mol wt (mass spectrum), 582 ($M^+ - 60$).

Deacetylacerotin (8).—A solution of acerotin (1, 13 mg) in EtOH (4 ml) and 2 *N* HCl (2 ml) was heated under reflux for 7 hr. The solution was concentrated and extracted with $CHCl_3$–EtOH. The extract was separated by tlc on silica gel ($CHCl_3$–EtOH 25:2) to give as gums 1 (6.5 mg), R_f 0.48, and 8 (3.0 mg): R_f 0.37; uv max 263 mμ (ε 27,900).

Deacetylacerocin (9).—Acerocin (2, 15 mg) was hydrolyzed in the same way as 1 to give as resins 2 (8.7 mg), R_f 0.48, and 9 (3.2 mg), R_f 0.37.

Diketone 16.—A solution of 8 (3.0 mg) in acetone (0.5 ml) was treated with 8 *N* CrO_3 in sulfuric acid at 0° for 70 min. Methanol was added and the solution was separated by tlc on silica gel ($CHCl_3$–EtOH 25:2) to give as a gum, the diketo acid 14 (2.1 mg): R_f 0.43; R_f (alumina, $CHCl_3$–EtOH 25:2) 0.01. 14 was placed on the origin of a silica gel tlc plate, which was then heated at 140° for 100 sec. The plate was developed ($CHCl_3$–EtOH 25:2) to yield as a gum, the diketone 16 (1.4 mg): R_f (silica gel, $CHCl_3$–EtOH 25:2) 0.75; R_f (alumina, $CHCl_3$–EtOH 25:2) 0.63; uv max 264 mμ (ε 25,000); ir ($CHCl_3$) 5.78, 5.88, and 6.10 μ; mass spectrum *m/e* 576, 422, 407, 394, 202, 137, 109. 1, 2, 8, and 9 were all stable under the pyrolysis conditions.

Diketone 17.—9 (3.2 mg) was oxidized in the same way as 8 to yield as a gum, the diketo acid 15 (1.9 mg): R_f (silica gel, $CHCl_3$–EtOH 25:2) 0.43; R_f (alumina, $CHCl_3$–EtOH 25:2) 0.01. Pyrolysis of 15 gave the diketone 17 (1.2 mg): R_f (silica gel, $CHCl_3$–EtOH 25:2) 0.75; R_f (alumina, $CHCl_3$–EtOH 25:2) 0.63; uv max 265 mμ (ε 17,100); ir ($CHCl_3$) 5.78, 5.88, 6.10, and 6.25 μ; mass spectrum *m/e* 576, 519, 422, 407, 394, 202, 137, 109.

Acetylacerotin (10). A. From Acerotin (1).—A solution of acerotin (9 mg) in acetic anhydride (0.2 ml) and pyridine (0.2 ml) was heated at 100° for 1 hr. Work-up followed by chromatography gave a gum 10 (8.6 mg): R_f (alumina, H_2O-saturated butanone) 0.49; R_f (silica gel, $CHCl_3$–EtOH 25:2) 0.53; uv max 264 mμ (ε 28,000); ir ($CHCl_3$) 5.74, 5.81, 5.83, 6.10, and 6.20 μ.

B. From Deacetylacerotin (8).—8 (5.5 mg) was acetylated as above to give 10 (4.3 mg), identical by ir spectroscopy and tlc to 10 derived from 1.

Alkaline Hydrolysis of Saponin P.—A solution of saponin P (6.6 mg) in 5% methanolic KOH was heated on a steam bath for 1 hr under nitrogen. The solution was concentrated *in vacuo*, acidified with 3 *N* HCl and extracted with hexane (4 ml), which was washed, dried, and evaporated. The residue was treated with diazomethane and the products were analyzed by vpc. The major components were 11 and 12 in a 1:1.5 ratio.

Hydrolysis of Saponin Q.—Saponin Q was hydrolyzed in the same way as saponin P. Vpc showed the presence of both 11 and 12 as major components.

Aglycone B.—A solution of saponin Q (250 mg) in EtOH (5 ml) and 2 *N* HCl (5 ml) was heated on a steam bath for 7 hr. The solution was diluted with water and extracted with chloroform, which was evaporated to yield a complex mixture of products (176 mg). The mixture was separated by tlc on silica gel ($CHCl_3$–EtOH 9:1) to yield as a homogeneous gum, aglycone B (12.9 mg): R_f 0.25; mp 190–196° dec; uv max 262 mμ (ε 25,300); ir (KBr) 2.9, 5.85, and 6.10 μ; mass spectrum *m/e* 640 (M^+, $C_{39}H_{60}O_7$), 424, 398, 137 (base peak), 109.

Sapogenin B (18). A. From Aglycone B.—A solution of aglycone B (7.2 mg) in 5% KOH in MeOH (2 ml) was refluxed for 1 hr. After concentration the solution was diluted with water acidified, and extracted with $CHCl_3$–EtOH. The organic layer was washed with water and evaporated to yield a solid (9.8 mg) which on tlc (silica gel, H_2O-saturated butanone) showed two spots. The upper spot absorbed uv light and corresponded to a C_9-unsaturated acid and the lower spot, R_f 0.60, was identical with that of sapogenin B.

On treatment with diazomethane the solid yielded sapogenin B methyl ester identical by tlc and ir spectroscopy with authentic material (see below).

B. From Saponin Q.—A solution of saponin Q (475 mg) in EtOH (10 ml) and 2 *N* HCl (10 ml) was refluxed for 6.5 hr. The solution was concentrated and partitioned between 1-butanol (20 ml) and water. The butanol-soluble fraction was dissolved in 5% KOH in MeOH (20 ml) and the solution refluxed for 1 hr under nitrogen. The solution was concentrated, diluted with water, acidified with 6 *N* HCl, and washed with petroleum ether. The aqueous solution was extracted with 1-butanol which was washed and evaporated to yield a resin. The resin was separated by tlc on silica gel (H_2O–saturated butanone) to give crude product (40 mg). Crystallization from aqueous MeOH and from methanol yielded sapogenin B (18): R_f 0.44; mp 341.5–342° dec; $[\alpha]^{24}D$ 70° (*c* 0.87, EtOH); uv end absorption 210 mμ (ε 4090); ir (KBr) 2.9 and 5.90 μ; mass spectrum *m/e* 504 (M^+). 486, 468, 458, 440, 424, 409, 391, 280, 262, 244, 234, 224, 217, 216.

Anal. Calcd for $C_{30}H_{48}O_6$: C, 71.39; H, 9.59. Found: C, 71.32; H, 9.58.

Sapogenin B Methyl Ester.—Sapogenin B (57 mg) was methylated using ethereal diazomethane and the product was purified by tlc on silica gel ($CHCl_3$–EtOH 10:1) to yield, after crystallization twice from aqueous methanol, the methyl ester: R_f 0.30; mp 228–229°; $[\alpha]^{24}D$ 68° (*c* 0.89, EtOH); ir (KBr) 2.9 and 5.86 μ; mass spectrum *m/e* 518 (M^+) 458, 294, 276, 234, 224, 217.

Anal. Calcd for $C_{31}H_{50}O_6 \cdot 0.5\ H_2O$: C, 70.55; H, 9.76. Found: C, 70.68; H, 9.54.

Sapogenin B Tetraacetyl Methyl Ester.—A solution of sapogenin B methyl ester (18 mg) in acetic anhydride (0.6 ml) and pyridine (0.6 ml) was kept at room temperature overnight. After heating at 100° for 30 min the solvent was evaporated. The residue was separated by tlc on silica gel ($CHCl_3$–MeOH 25:1). The major product was crystallized from methanol to yield the methyl ester tetraacetate (17 mg): R_f 0.6; mp 230–232°; $[\alpha]^{24}D$ 48° (*c* 0.73, $CHCl_3$); ir (KBr) 5.71, 5.75, and 5.77 μ.

Anal. Calcd for $C_{39}H_{58}O_{10}$: C, 68.19; H, 8.51; mol wt, 686. Found: C, 68.25; H, 8.56; mol wt (mass spectrum), 686.

Acetonide of Sapogenin B Methyl Ester.—A solution of sapogenin B methyl ester (9.8 mg) in acetone (1 ml) was treated with 70% perchloric acid (1 drop) and left at room temperature for 6 hr. The solution was basified with 5% aqueous $NaHCO_3$ and evaporated. The residue was extracted with chloroform which on evaporation yielded a gum. Separation by tlc on silica gel ($CHCl_3$–EtOH 10:1) yielded an amorphous acetonide (5.1 mg): ir ($CHCl_3$) 2.80, 5.80, 5.86, and 6.25 μ; mass spectrum *m/e* 558, 530, 500, 470, 441, 294, 276, 258, 244, 234, 217.

Anal. Calcd for $C_{34}H_{54}O_6$: mol wt, 558.3920. Found: mol wt (mass spectrum), 558.3927.

Registry No.—1, 29038-22-0; 2, 29038-41-3; 3, 29038-42-4; 4, 29168-37-4; 5, 29038-43-5; 6, 29206-67-5; 8, 29246-41-1; 10, 29168-40-9; 11, 29038-44-6; 12, 29038-45-7; 13, 29168-43-2; 14, 29246-42-2; 15, 29168-44-3; 16, 29168-45-4; 17, 29168-46-5; 18, 29168-47-6; 18 methyl ester, 29246-43-3; 18 tetraacetyl methyl ester, 29168-48-7; 18 acetonide methyl ester, 29246-44-4; 19, 29168-49-8.

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Molecular Spectra and Conformations of Conjugated Dienones

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An extensive series of conjugated dienones has been studied using infrared, nmr, and uv spectroscopy. *all-trans*-Dienones have *s-trans*-diene units and exist as equilibrium mixtures of *s-cis*- and *s-trans*-enone conformers. β substitution leads to an entirely *s-cis*-enone unit while α substitution results in an *s-trans*-enone unit. α,β-*cis*-γ,δ-*trans*-Dienones have *s-trans*-diene and *s-cis*-enone units. Both *all-trans*- and *cis,trans*-dienones normally are planar-conjugated molecules. Highly substituted *all-trans*-dienones like 4,6-dimethylheptadienone (16) and β-ionone are almost certainly significantly out of planarity. α,β-*cis*-Dienones which have no stable planar conformation exist as the valence isomeric α-pyrans. α,β-*trans*-γ,δ-*cis*-Dienones exist as mixtures of *s-cis*- and *s-trans*-enone conformers both with *s-trans*-diene units and may deviate slightly from planarity. *cis*-δ-Phenyl groups are twisted out of the diene plane. 1-Phenyl dienones have *s-cis*-enone and *s-trans*-diene units. Small deviations from planarity, <25°, would not be revealed by our data.

As part of a thorough study of photoisomerization reactions of α-, β-, γ-, δ-unsaturated ketones,[2] we have pursued spectroscopic investigations as a means of identification and in an attempt to specify details of conformations. Aside from rigid steroidal dienones[3] and cyclohexadienones,[4] very little spectroscopic data on conjugated dienones have been reported in the literature. Numerous spectroscopic studies of the closely related α,β-unsaturated ketones have been published, and the important observations and structural conclusions are summarized below.

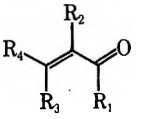
Rigid *s-trans*-enones (1) generally exhibit two bands in the 1600–1700-cm^{-1} region.[5,6] Rigid *s-cis*-enones (2) also exhibit two bands in this region, but, owing to stronger coupling of the C=O and C=C stretching vibrations,[7] their separation is greater than in the s-trans cases. The ratio of integrated absorption intensities

1

2

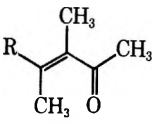
$\epsilon_{CO}/\epsilon_{CC}$ varies from 0.6 to 3.5 for *s-cis*-enones and is greater than 3 for the s-trans compounds.[5-10] $\nu_{CO\text{s-cis}} - \nu_{CO\text{s-trans}}$ is approximately constant at +20–25 cm^{-1}.[5-10] Many conformationally flexible enones exhibit up to four absorption bands in the 1600–1700-cm^{-1} region, indicating the presence of both s-cis and s-trans conformers.[5,6,8-13] Noack and Jones have demonstrated by variable-temperature studies of *trans*-3-pentenone that the multiplicity of bands was not caused by Fermi resonance and that the s-trans conformer was more stable than the s-cis.[13]

Conformational conclusions drawn from these studies can be summarized as follows.[13] The s-cis and s-trans



3

conformers of **3** will exist in equilibrium when R_2 and R_3 = H and R_1 is less bulky than *tert*-butyl. If R_3 is alkyl or if R_1 = *tert*-butyl,[9] steric interactions destabilize the s-trans conformer to the extent that it is not detected. If R_1 and R_2 are alkyl, the s-cis conformer is destabilized, and only the s-trans is detected. When R_1, R_2, R_3, and R_4 are all alkyl groups, nonplanar conformations probably result. Several groups have remarked that such compounds exhibit abnormally broad C=C bands and attributed this fact to nonplanarity.[5,12] This conclusion finds support in the ^{13}C nmr studies of Marr and Stothers who showed that shielding of the carbonyl carbon was normally independent of conformation but that the carbonyl carbons of **5a** appeared at significantly lower field than usual.[14]



5a, R = CH_3
b, R = CH_2CH_3

Nmr spectroscopy has proven to be of great value in determining the stereochemistry of acyclic enones.[15] β-Methyl groups and hydrogens which are cis to the carbonyl group are significantly more deshielded than their trans counterparts.[12,15] Data on rigid enones[15] and the study of Kossanyi[12] show clearly that deshielding of the cis β substituent is associated with the presence of the s-cis conformation and is presumably caused by the long-range anisotropic effect of the carbonyl group. Faulk and Fry have shown that in "peralkyl" enones (**3**, R_1–R_4 = alkyl) the chemical shift difference between cis and trans β-methyl groups disappears, presumably owing to the twisting of the carbonyl out of the double-bond plane.[16] Ultraviolet spectra of enones have long been used in structure proof owing to the sensitivity of their π,π^* absorption

(1) (a) NSF Trainee, 1965–1969; (b) Alfred P. Sloan Foundation Fellow, 1969–1971.

(2) A. F. Kluge and C. P. Lillya, *J. Org. Chem.*, **36**, 1988 (1971).

(3) (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 20, report uv data. (b) R. N. Jones, P. Humphries, and K. Dobriner, *J. Amer. Chem. Soc.*, **72**, 956 (1950), report ir data.

(4) *Cf.* E. C. Friederich, *J. Org. Chem.*, **33**, 413 (1968), who reports ir, nmr, and uv data.

(5) R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).

(6) R. Mecke and K. Noack, *Chem. Ber.*, **93**, 210 (1960).

(7) K. Noack, *Spectrochim. Acta*, **18**, 1625 (1962).

(8) R. Mecke and K. Noack, *ibid.*, **12**, 391 (1958).

(9) M. E. Kronenberg and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **84**, 17 (1965).

(10) W. P. Hayes and C. J. Timmons, *Spectrochim. Acta, Part A*, **24**, 323 (1968).

(11) C. J. Timmons, *et al.*, paper presented at the Fourth International Meeting of the European Molecular Spectroscopy Group, Bologna, Italy, 1959; *cf.* ref 5.

(12) J. Kossanyi, *Bull. Soc. Chim. Fr.*, 704 (1965).

(13) K. Noack and R. N. Jones, *Can. J. Chem.*, **39**, 2225 (1961).

(14) D. H. Marr and J. B. Stothers, *ibid.*, **43**, 596 (1965).

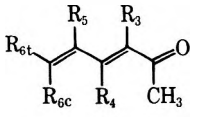
(15) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, 2nd ed., Pergamon Press, London, 1969, pp 91, 222–223.

(16) D. D. Faulk and A. Fry, *J. Org. Chem.*, **35**, 364 (1970).

maxima to structure.[17] Braude and Timmons[18] have interpreted the reduced absorption intensity of some enones which are hindered in their s-trans conformations in terms of nonplanarity. However, Mecke and Noack[6,8] have pointed out that this interpretation is inconsistent with ir evidence for the existence of a nearly planar s-cis conformation for some of these compounds. It now seems clear that the reduced absorption intensity is associated with preferred s-cis conformations[6,17] and that only severely hindered compounds such as **5a** and **5b** are nonplanar.

Infrared Spectra.—Carbonyl and carbon–carbon double-bond infrared stretching frequencies for a number of dienones are listed in Table I. Addition of a second conjugated double bond modifies the enone stretching frequencies relatively little, carbonyl frequencies being only 8–10 cm^{-1} lower in dienones than in enones.[19] Thus in analogy to enones we have interpreted bands above 1650 cm^{-1} as carbonyl bands and those at lower frequency as C=C bands. Compounds **17**, **18**, and **30** which have rigid *s-trans*-enone moieties exhibit single carbonyl absorptions at 1670, 1669, and 1660 cm^{-1}, respectively. Jones *et al.*,[19] found $\nu_{CO}(CS_2)$ 1663–1669 cm^{-1} for several rigid all-s-trans steroidal dienones.[20] The two carbonyl bands exhibited by 3-(*trans*-β-styryl)-2-cyclohexenone (**29**) are probably caused by Fermi resonance involving the overtone of the out-of-plane stretching frequency of the α-olefinic hydrogen as has been clearly demonstrated for a number of cyclohexenones.[21]

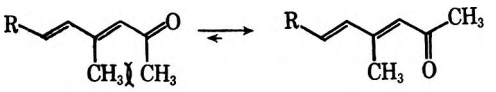
trans,trans-3,5-Heptadienone (**6**) gives a spectrum which is typical of many flexible *α,β-trans*-dienones. Its two carbonyl absorptions at 1690 and 1670 cm^{-1} are in the right regions for *s-cis*- and *s-trans*-enone conformers, respectively. The 3,5-deuterio derivative, **6-*3,5-d*$_2$**, also exhibits two carbonyl absorptions, ruling out Fermi resonance (*vide supra*) as a cause of band multiplicity.[21] A similar demonstration has been made in the case of *trans,trans*-cinnamylideneacetone (**22**) and **22-*2-d***. In this case the three maxima in the carbonyl region by **22** are reduced to two upon α-deuteration (**22-*2-d***). Thus, the infrared evidence shows clearly that flexible *α,β-trans*-dienones in which the α and β substituents, R_3 and R_4 in **45**, are hydrogen exist as mixtures of *s-trans*- and *s-cis*-enone conformers.[22] Typical carbonyl stretching frequencies



45

seem to be $\nu_{CO}^{CCl_4}$(s-trans) 1660–1670 cm^{-1} and $\nu_{CO}^{CCl_4}$(s-cis) 1680–1690 cm^{-1}. The difference between ν_{CO}(s-cis) and ν_{CO}(s-trans) of 18–21 cm^{-1} is in good agreement with that observed for simple enones.

As in the case with enones, when R_4 = CH_3, the

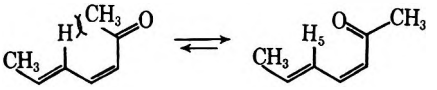


46 **47**

R = CH_3, C_6H_5

s-trans conformation is destabilized by a 1,3 methyl–methyl interaction[23] (**46**) and only the s-cis conformer (**47**) is detected. Thus, compounds **25** and **26** exhibit single carbonyl absorptions in the s-cis region.[24] When R_3 = CH_3 (**15**), only the s-trans conformer is detected with ν_{CO} 1665 cm^{-1}.

α,β-cis-Dienones would be expected to be unstable in their s-trans conformations (**7a**). In agreement with



7a **7**

expectation, the *α,β-cis*-dienones **7**, **10**, **12**, **23**, and **27** all exhibit single carbonyl absorptions in the s-cis region.

These infrared data and the conformational conclusions based upon them are consistent in all details with those from simple enones. The additional double bond of the dienones clearly does not perturb the carbonyl stretching vibrations in any drastic way. In contrast to the carbonyl absorptions, the C=C absorptions do not seem to depend on molecular structure in a simple fashion and are of no real use in the deduction of conformation. In agreement with the above vinology principle, the carbonyl absorptions of the trienones **41**, **42**, **44**, and **45** mirror those of their dienone analogs. 6-Phenyl-3,5,7-octatrien-2-one (**43**) would be expected to exhibit separate carbonyl absorptions for its *s-cis*- and *s-trans*-enone conformers (*cf.* dienones **22** and **22-*2-d***), but only one absorption at 1660 cm^{-1} corresponding to an s-trans conformer is observed.

Nmr Spectra.—Nmr data for a series of dienones, deduced by first-order analysis, are listed in Table II. Coupling constants and exact chemical shifts have not been specified for non-first-order spectra. In many cases assignments have been made unambiguously on the basis of specific deuterium labeling or signal multiplicity. These assignments have provided a sound basis for assignment of the remaining signals by process of elimination or by analogy. Details of important assignments are discussed below.

In general, the H_3 signal is the farthest upfield of all the olefinic hydrogen signals. Unambiguous assignment of the H_3 signal by means of specific deuterium labeling has been accomplished for **6** and **22**. Compound **6-*2,5-d*$_2$** was prepared as shown in eq 1. Incorporation of deuterium at C_5, presumably during the Perkin condensation, was apparent from the nmr spectrum of the tricarbonyl iron complex of **6-*3,5-d*$_2$**.[25] The nmr spectrum of **6-*3,5-d*$_2$** at 60 MHz reveals a greatly diminished upfield doublet which is partially merged with signals from H_{6c} and H_5 on its low-field side.[26]

(17) *Cf.* A. I. Scott, "Interpretation of the Ultra-Violet Spectra of Natural Products, Pergamon Press, London, 1964, pp 57–63.

(18) E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 3766 (1955).

(19) (a) E. R. Blout, M. Fields, and R. Karplus, *J. Amer. Chem. Soc.*, **70**, 194 (1948); (b) R. N. Jones, P. Humphries, and K. Dobriner, *ibid.*, **72**, 956 (1950).

(20) Three compounds: two $\Delta^{4,6}$-3-ones and one $\Delta^{3,5}$-7-one.

(21) (a) K. Noack, *Spectrochim. Acta*, **18**, 697 (1962); (b) H. N. A. Al-Jallo and E. S. Waight, *J. Chem. Soc. B*, 73 (1966).

(22) Only **24** does not exhibit the expected doubling of the carbonyl absorption, and its carbonyl band is broad.

(23) The 1,3 methyl–methyl and 1,3 methyl–hydrogen interactions have been estimated as 7.6 and 1.6 kcal/mol, respectively, in 1,8-substituted naphthelene-type structures: J. Packer, J. Vaughan, and E. Wong, *J. Amer. Chem. Soc.*, **80**, 905 (1958).

(24) Compound **11** exhibits a principal maximum in the s-cis region at 1677 cm^{-1} but has several shoulders in the carbonyl region as well.

(25) C. P. Lillya and R. A. Sahatjian, *J. Organometal. Chem.*, in press.

(26) The spectrum of **6** has been discussed previously: N. A. Clinton and C. P. Lillya, *J. Amer. Chem. Soc.*, **92**, 3065 (1970).

TABLE I
INFRARED AND ULTRAVIOLET ABSORPTION OF DIENONES

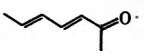
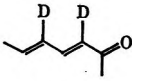
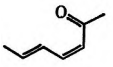
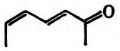
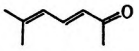
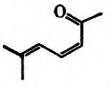
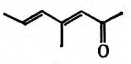
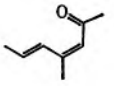
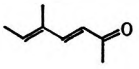
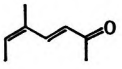
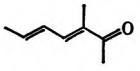
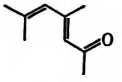
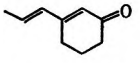
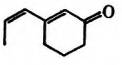
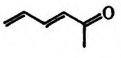
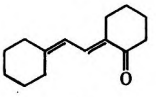
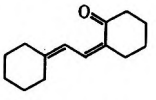
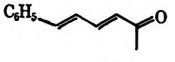
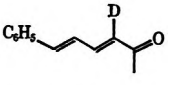
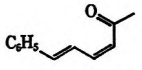
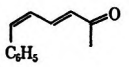
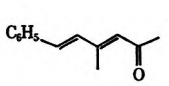
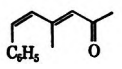
	Compound	Infrared[a]		Ultraviolet		
		ν_{CO} (cm^{-1})	ν_{CC} (cm^{-1})	λ_{max} (nm)	ϵ_{max}	Solvent
6		1690, 1670 1685, 1665[b]	1643, 1596	265 270	28,950 28,500	C_6H_{12} EtOH[c]
6-3,5-d_2		1685 (sh), 1667	1630, 1594, 1582			
7		1690	1634, 1580	273 279	13,960 10,400	C_6H_{12} 95% EtOH
8		1691, 1673	1630, 1595	267 273 (sh)	22,400 20,900	C_6H_{12}
9		1685, 1667[b]	1635, 1590[b]	278 286	27,000 22,400	C_6H_{12} EtOH[d]
10		1680[b]	1625, 1574[b]	286	22,700	C_6H_{12}
11		1710 (sh), 1677, 1670 (sh), 1650 (sh)	1634, 1585	272.5	22,800	C_6H_{12}
12		1680	1638, 1580	279	7,360	C_6H_{12}
13		1695 (sh), 1666[b]	1622[b]	267.5	28,300	C_6H_{12}
14		1686, 1670	1628, 1588	273.5 279 (sh)	18,250 17,860	C_6H_{12}
15		1665[b]	1640, 1601[b]	269	28,200	C_6H_{12}
16		1680[b]	1632, 1595, 1580[b]	276	10,000	C_6H_{12}
17		1670	1642, 1590	260	33,500	C_6H_{12}
18		1669	1631, 1608, 1581	265	21,800	C_6H_{12}
19				258	32,500	CH_3OH[e]
20				310 297	22,500 25,300	EtOH[f] Et_2O[g]
21				305	15,200	EtOH[f]
22		1693, 1676, 1657	1626, 1615, 1601, 1592	310 233 319	38,000 7,900 36,200	C_6H_{12} EtOH[h]
22-3-d		1686, 1665	1621, 1605, 1589, 1582, 1570			
23		1685	1615, 1581, 1568	323.5 226	32,100 10,900	C_6H_{12}
24		1652[b]	1609, 1583[b]	299 225	12,600 12,600	C_6H_{12}
25		1681	1580	317 243 235 323 237	30,800 6,300 7,500 24,500 8,500	C_6H_{12} EtOH[i]
26		1685	1600, 1590	296.5 236	9,830 11,200	C_6H_{12}

TABLE I (*Continued*)

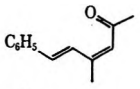
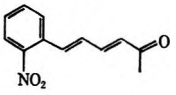
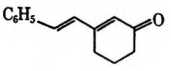
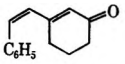
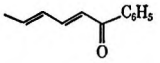
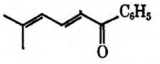
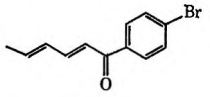
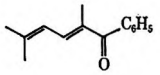
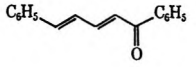
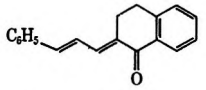
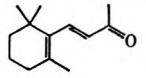
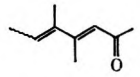
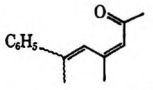
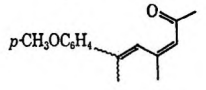
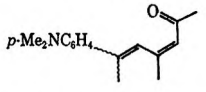
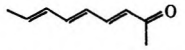
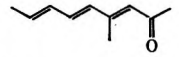
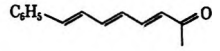
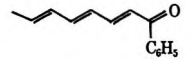
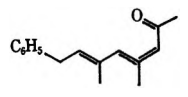
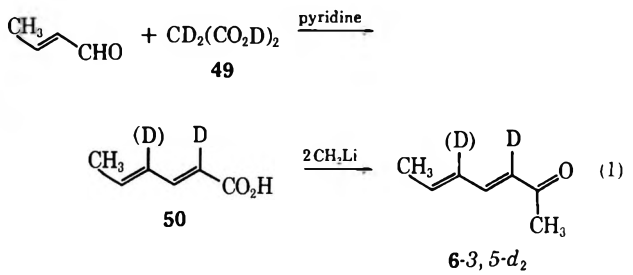
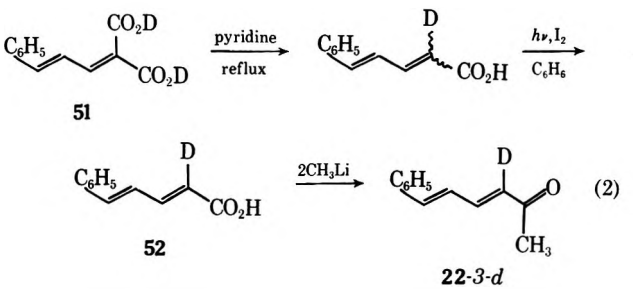
	Compound	Infrared[a] ν_{CO} (cm^{-1})	Infrared[a] ν_{CC} (cm^{-1})	Ultraviolet λ_{max} (nm)	Ultraviolet ϵ_{max}	Solvent
27		1675[b]	1615, 1580, 1570[b]	321	23,900	C_6H_{12}
28				292 220	23,000 9,570	C_6H_{12}
29		1675 (sh), 1665	1622, 1600, 1586	312 240 233 323 235	39,400 8,700 9,900 25,500 11,250	C_6H_{12} EtOH[j]
30		1660	1620, 1601, 1580	285 232	14,400 10,900	C_6H_{12}
31		1670	1635, 1601, 1595, 1585 (sh)	288 297	21,700 19,500	C_6H_{12} EtOH[h]
32		1665	1630, 1601 1587, 1577 (sh)	308 315 219	27,600 25,000 9,500	C_6H_{12} EtOH[q]
33		1668	1632, 1593	292 298 302.5	29,400 29,400 29,000	C_6H_{12} EtOH
56a				302	27,600	EtOH[r]
34		1663	1602, 1586	330 343 342	39,800 35,500 38,900	C_6H_{12} EtOH CH_3OH[k]
35		1668	1609, 1582	343 355	35,400 28,500	C_6H_{12} EtOH
36				295	10,700	EtOH[l]
37				281	14,400	EtOH[m]
38		1685[m]	1599	302.5	11,700	CH_3OH[n]
39		1685[m]	1600	292.5	10,900	CH_3OH[n]
40		1681[m]	1612	370 268	17,900 12,900	CH_3OH[n]
41		1681 (sh), 1663[b]	1640, 1611, 1580[b]	308 297	40,300 41,000	n-C_6H_{14}[o]
42		1672[b]	1640, 1596, 1570[b]	320 307	29,200 35,300	C_6H_{12}
43		1660[k]	1605, 1595, 1580, 1570[k]	342	49,000	Et_2O[p]
44		1664	1601, 1576	336 (sh) 325 264 247 238 232 340 268	24,100 24,900 10,900 11,450 12,200 11,600 36,600 10,270	C_6H_{12} EtOH[o]
45		1683	1598	341.5	17,900	CH_3OH[n]

TABLE I (*Footnotes*)

[a] Ambient temperature, all spectra in carbon tetrachloride solution unless otherwise specified. [b] Neat liquid between sodium chloride disks. [c] S. Heilbron, E. R. H. Jones, and R. W. Richardson, *J. Chem. Soc.*, 287 (1949). [d] G. Martin, *Ann. Chim.* (*Paris*), **4**, 541 (1959). [e] R. F. Heck, *J. Amer. Chem. Soc.*, **85**, 3383 (1963). [f] I. T. Harrison and B. Lythgoe, *J. Chem. Soc.*, 837 (1958). [g] K. Dimroth, *Chem. Ber.*, **71**, 1346 (1938). [h] R. Kuhn and H. A. Staab, *ibid.*, **87**, 262 (1954). [i] C. H. Eugster, C. Garbers, and P. Karrer, *Helv. Chim. Acta*, **35**, 1179 (1952). [j] J. M. Conia and U. O'Leary, *C. R. Acad. Sci.*, Ser. B, **249**, 1002 (1959). [k] J. F. Thomas and G. Branch, *J. Amer. Chem. Soc.*, **75**, 4793 (1953). [l] Y. R. Naves, *Helv. Chim. Acta*, **31**, 893 (1948). [m] J. Royer and J. Dreux, *Tetrahedron Lett.*, 5589 (1968). [n] G. Kobrich and D. Wunder, *Justus Liebigs Ann. Chem.*, **654**, 131 (1962). [o] M. Kröner, *Chem. Ber.*, **100**, 3172 (1967). A preparation of ours exhibited the same spectrum but with low ϵ values (*ca.* 27,000). The cause of this discrepancy is under investigation. [p] D. J. Zepka, Ph.D. Thesis, University of Massachusetts, 1969. [q] J.-P. Montillier and J. Dreux, *Bull. Soc. Chim. Fr.*, 3638 (1969). [r] A. Duperrier and J. Dreux, *Tetrahedron Lett.*, 3127 (1970).



At 100 MHz the H_3 doublet of **6** is fully resolved, and double resonance experiments show clearly that H_3 is coupled to H_4 which appears downfield at τ 2.93. Preparation of *22-3-d* was accomplished as shown in eq 2. The nmr spectrum of *22-3-d* was similar to that



of **22** in all major respects except that the upfield doublet at τ 3.85 was almost completely absent. Assignment of the upfield olefinic signal to H_3 also finds support from assignments based on spin–spin coupling patterns. The one-hydrogen singlets in the olefinic region exhibited by **17**, **25**, **26**, **29**, and **30** must be due to H_3. The H_3 signal in **16** can be assigned on the basis of allylic coupling with the 4-methyl group. Finally the 5-methyl compounds **13** and **14** exhibit two widely spaced olefinic doublets which can be assigned with confidence to H_3 and H_4 by analogy.

Assignment of the H_3 signal makes possible determination of the vicinal coupling constant J_{34} and allows unambiguous assignment of configuration about the α,β (3,4) double bond.[27] Compounds **6**, **8**, **9**, **12–14**, **22**, **24**, and **31–33** with J_{34} = 15–16 Hz clearly have α,β-trans configurations while **10** and **23** with J_{34} = 12 Hz have α,β-cis configurations.

The H_4 signal is the lowest field olefinic signal in α,β-*trans*-dienones and is well resolved in the spectra of the aliphatic compounds. The assignment has been made unambiguously for **6** on the basis of deuterium labeling and double resonance (*vide supra*). Spin–spin splitting patterns make assignment of H_4 clear in **9**, **13**, **14**, and **15**. As is the case with enones,[12,15] some of the deshielding of H_4 is attributable to the anisotropic effect of the carbonyl group when the enone unit is in the s-cis conformation. Thus, **6** and **13**, which infrared spectroscopy reveals as mixtures of *s-cis*- and *s-trans*-enone conformers, exhibit H_4 signals at τ 2.93 and 2.91, while **15**, which infrared shows to be entirely s-trans, exhibits an H_4 signal at *ca.* 0.15 ppm to higher field. A further effect on the chemical shift of H_4 is the deshielding by 0.3–0.4 ppm associated with the presence of a methyl group in the 6*c* position (**8**, **9**, **14**, and **32**). Among the possible causes of the deshielding are the direct field and van der Waals effects[23] of the methyl group.[28] Methyl groups in the 4 position are strongly deshielded in agreement with enone data[12,15] and with our conclusions based on infrared evidence that these compounds (**11**, **16**, **25**, and **26**) have *s-cis*-enone units.

In α,β-*cis*-dienones H_4, no longer affected by carbonyl anisotropy, appears at higher field; and it is H_5, dramatically deshielded by the carbonyl group, which appears at lowest field. In **7** and **23** quartets at τ 2.48 and 1.86 respectively (J_{45} = 12, J_{56c} = 15 Hz) are assigned to H_5 because of the large trans vicinal coupling.[27] The H_4 signal should be a near triplet with both J_{34} (cis) and J_{45} = ~12 Hz. The doublet for H_5 in **10** was assigned on the basis of its broadening owing to allylic coupling with the 6-methyls. In **12** only H_5 can give a doublet (τ 2.41), and in **27** the doublet at τ 1.64 is assigned to H_5 rather than H_{6c} by analogy.[29] The large downfield shift of H_5 which occurs when the configuration of the α,β bond is changed from trans to cis is consistent only with planar α,β-*cis*-dienones possessing *s-cis*-enone and *s-trans*-diene conformations (see **7**). Strong deshielding of H_5 owing to carbonyl anisotropy is predicted in conformation **7** by the Pople model.[30–32] An analogous effect in the dienone tagatone (**53**, see Table II) has been described by Bishop and Musher,[34] and similar deshielding in an α,β-*cis*-dienoic ester has also been described.[35] The s-cis conformation of the enone unit in the α,β-*cis*-dienones is in full accord with their infrared carbonyl stretching frequencies.

The nmr spectra also provide definitive information about diene conformation which is not available from infrared spectra. From the value of J_{45} = 10–12 Hz in **6–10**, **15**, **23**, **24**, and **32**, it is clear that their diene units

(27) *Cf.* A. A. Bothner-By, *Advan. Magn. Resonance* **1**, 207 (1965).

(28) Reference 15, p 71.

(29) This leaves a doublet at τ 3.20 to be assigned as H_{6c} in agreement with the τ 3.1 shift of H_{6c} in the closely analogous compound **25**.

(30) Reference 15, p 88.

(31) J. A. Pople, *J. Chem. Phys.*, **37**, 60 (1962).

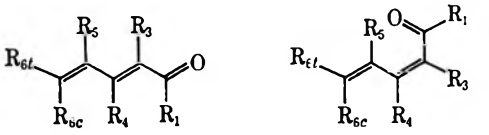
(32) Deshielding of H_3 does not seem consistent with the shielding model constructed by Karabatsos, *et al.*,[33] using the carbonyl anisotropies of Ap-Simon, *et al.* In contrast the relative shielding of H_3 with respect to the other olefin hydrogens seems in accord with the Karabatsos model but not with that of Pople. In fact Jackman and Sternhell[15] have observed that no single model for carbonyl shielding accounts adequately for all the available data.

(33) G. J. Karabatsos, G. D. Sonnichsen, N. Hsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **89**, 5067 (1967).

(34) E. O. Bishop and J. I. Musher, *Mol. Phys.*, **6**, 621 (1963).

(35) G. Englert, *Z. Anal. Chem.*, **181**, 447 (1961).

TABLE II
NMR SPECTRA OF DIENONES[a]



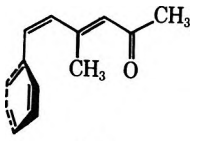
I II

Compound		Chemical shifts in τ units[c] and signal multiplicity[d]						
No.	Structure[b]	R_1	R_3	R_4	R_5	R_{6c}	R_{6t}	Coupling constants,[e] Hz
6	I, $R_{1,6t} = CH_3$	7.82 s	4.00 d	2.93 o	~3.9 m	~3.9 m	8.18 d	$J_{34} = 15$, $J_{45} = 10$, $J_{6c6t} = 4.5$
6-*3,5-d*	I, $R_{1,6t} = CH_3$; $R_{3,5} = D$	7.85 s	...	~3.0 b	...	~3.9 m	8.18 d	$J_{6c6t} = 6$
7	II, $R_{1,6t} = CH_3$	7.85 s	~4.05	~3.6	2.48 q	~3.85	8.17 d	$J_{45} = 12$, $J_{56c} = 15$, $J_{6c6t} = 7$
8	I, $R_{1,6c} = CH_3$	7.82 s	~4	2.64 q	~4	8.12 d	~4	$J_{34} = 16$, $J_{45} = 10.5$, $J_{6c6t} = 5.5$
9	I, $R_{1,6c,6t} = CH_3$	7.80 s	4.05 d	2.60 q	4.05 d	8.10 s	8.10 s	$J_{34} = 15$, $J_{45} = 11$
10	II, $R_{1,6c,6t} = CH_3$	7.89 s	4.20 d	3.45 t	2.81 d, b	8.12 s[f]	8.18 b[f]	$J_{34} = 12$, $J_{45} = 12$, $J_{56c} \leq 1^g$
11	I, $R_{1,4,6t} = CH_3$	7.88 s	~3.9	7.83 s	~3.9	~3.9	8.17 d	$J_{6c6t} = 5$
12	II, $R_{1,4,6t} = CH_3$	7.90 s	4.10 s, b	8.07 s, b	2.41 d, b	3.88 o	8.17 d, b	$J_{56c} = 15$, $J_{6c6t} = 4.5$
13	I, $R_{1,5,6t} = CH_3$	7.83 s	4.03 d	2.91 d	8.26 s, b	4.06 q, b	8.22 d	$J_{34} = 16$, $J_{6c6t} = 6$
14	I, $R_{1,5,6c} = CH_3$	7.78 s	3.96 d	2.47 d	8.17 s, b	8.13 d	4.2 q, b	$J_{34} = 16$, $J_{6c6t} \sim 6$
15	I, $R_{1,3,6t} = CH_3$	7.78 s	8.19 s	3.08 d	~3.7 m	~3.9 m	8.11 d	$J_{45} = 10$
16	I, $R_{1,4,6c,6t} = CH_3$	7.90 s	4.30 s, b	7.87 d	4.03 s, b	8.17 s	8.17 s	$J_{34} \sim 1^g$
17	I, $R_{1,4} = (CH_2)_3$; $R_{6t} = CH_3$[h]	7.5–8.1 m	4.30 s	7.5–8.1 m	3.95 m	3.95 m	8.16 d	$J_{6c6t} = 5$
18	I, $R_{1,4} = (CH_2)_3$, $R_{6c} = CH_3$[h]	7.3–8.1 m	~4.2	7.3–8.1 m	~4.2	8.14 d	~4.2	$J_{6c6t} = 5$
22	I, $R_1 = CH_3$; $R_{6t} = C_6H_5$	7.82 s	3.85 d	~2.7	~3.1	~3.1	2.6 m	$J_{34} = 15$
22-*3-d*	I, $R_1 = CH_3$; $R_{6t} = C_6H_5$; $R_3 = D$	7.80 s	...	~2.7	~3.1	~3.1	2.6 m	
23	II, $R_1 = CH_3$; $R_{6t} = C_6H_5$	7.84 s	4.05 d	3.55 t	1.86 q	3.29 d	2.7 m	$J_{34} = 12$, $J_{45} = 12$, $J_{56c} = 15$
24	I, $R_1 = CH_3$; $R_{6c} = C_6H_5$	7.82 s	3.87 d	~2.7	3.68 t	2.61 s	3.08 d	$J_{34} = 16$, $J_{45} = 11$, $J_{56t} = 11$
25	I, $R_{1,4} = CH_3$; $R_{6t} = C_6H_5$	7.87 s	3.85 s, b	7.70 d	3.35 d	3.1 d	2.7 m	$J_{34} = 1.5$,[g] $J_{56c} = 16$
26	I, $R_{1,4} = CH_3$; $R_{6c} = C_6H_5$	7.98 s	3.87 s, b	7.94 s, b	3.95 d	2.8 s	3.46 d	$J_{56t} = 12$
27	II, $R_{1,4} = CH_3$; $R_{6t} = C_6H_5$	7.92 s	3.95 s, b	8.04 d	1.64 d	3.20 d	2.7 m	$J_{34} = 1$,[g] $J_{56c} = 16$
29	I, $R_{1,4} = (CH_2)_3$[i] $R_{6t} = C_6H_5$	7.3–8.1 m	4.02 s	7.3–8.1 m	3.12 s	3.12 s	2.65 m	
30	I, $R_{1-4} = (CH_2)_3$; $R_{6c} = C_6H_5$	7.3–8.1 m	4.10 s	7.3–8.3 m	3.73 d	2.78 s	3.31 d	$J_{56t} = 12$
31	I, $R_1 = C_6H_5$; $R_{6t} = CH_3$	2.1–2.9 m	3.18 d	~2.7	3.9 m	3.9 m	2.13 t[j]	$J_{34} = 15$
32	I, $R_1 = C_6H_5$; $R_{6c,6t} = CH_3$[l]	2.2–3.0 m	3.23 d	2.39	3.96 d[k]	8.12 b	8.12 b	$J_{34} = 15$, $J_{45} = 12$, $J_{\text{Allylic}} \backsim 1^{g-k}$
56a	I, $R_1 = C_6H_5$; $R_{3,6c,6t} = CH_3$[m]	2.3–2.7 m	7.99	3.02	3.77	8.12	8.33	$J_{45} = 11$, $J_{34} = 1.4$,[g] $J_{56} = 1.3^g$
56b	I, $R_1 = C_6H_5$; $R_{5,6c,6t} = CH_3$[n]	2.0–2.3 2.4–2.8 m	3.15 d	2.04 d	8.08 s	8.17 s	8.17 s	$J_{34} = 15$
33	I, $R_1 = p\text{-}BrC_6H_4$; $R_{6t} = CH_3$	2.25–2.55 m	3.29 d	2.68 q	~3.8 m	~3.8 m	8.10 d	$J_{34} = 15$, $J_{6c6t} = 5$, $J_{45} \backsim 10$
53	II, $R_1 = i\text{-}Bu$; $R_4 = CH_3$[n]		3.93 s, b		2.06 o	5.57 m	5.34 m	$J_{56c} = 10.9$, $J_{56t} = 17.7$, $J_{36c} = 1.5$, $J_{6c6t} = 1.3$

[a] As *ca.* 10% solutions in carbon tetrachloride unless otherwise noted. [b] Only substituents other than ^1H are listed. [c] Chemical shifts relative to internal tetramethylsilane. [d] s = singlet, d = doublet, t = triplet, q = quartet, o = octet, m = multiplet, b = broadened. [e] Coupling constants are based on first-order analysis and should be reliable within ±1 Hz in most cases. [f] Assignment of 6-methyls is based on the expectation that *cis*-allylic coupling with H_5 will be larger than *trans*-allylic coupling; *cf.* ref 15, pp 316–324. [g] Allylic coupling constant. [h] In deuteriochloroform. [i] D. E. Kuhn, Ph.D. Thesis, University of Massachusetts, 1969. [j] The unusual triplet multiplicity is probably caused by virtual coupling effects; *cf.* ref 26. [k] Each peak of the H_5 doublet appears as a symmetrical pentuplet with a line separation of *ca.* 1 Hz. This requires that H_5 be nearly equally coupled to both the *cis*- and *trans*-methyl hydrogens. [l] An essentially identical spectrum is reported in footnote *m*. [m] J.-P. Montillier and J. Dreux, *Bull. Soc. Chim. Fr.*, 3638 (1969). [n] Parameters based on complete analysis of a spectrum of the neat dienone at 29.914 MHz (ref 34).

are in the expected[36] s-trans conformation.[37] Typical vicinal coupling across the essential single bond of *s-cis*-dienes is only 5–7 Hz.[37b,38] The large J_{45} values suggest that the *s-trans*-diene units of both α,β-*cis*- and α,β-*trans*-dienones do not deviate very much from planarity.[37b]

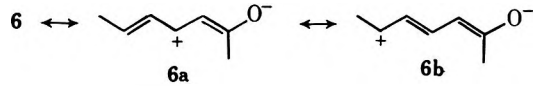
Conformations of 6-phenyl substituents can also be deduced from the nmr data. Compounds **22**, **23**, **25**, **27**, and **29**, which bear a phenyl group in the 6*t* position, all exhibit the complex multiplet of a conjugated phenyl group.[39] In contrast, **24**, **26**, and **30**, which bear a phenyl group in the more crowded 6*c* positon, all exhibit sharp singlets characteristic of unconjugated phenyl groups.[39] Therefore, in the γ,δ-cis compounds the δ-phenyl group is twisted out of the dienone plane, owing to steric interactions. The pronounced upfield shift of the 4-methyl group (0.28 ppm) on going from **25** to its γ,δ-cis isomer **26** can be attributed to long-range shielding by the out-of-plane phenyl group (**26a**).



26a

The value of J_{34} = 11 Hz in **24** shows that at least in this case the diene unit remains close to planarity.

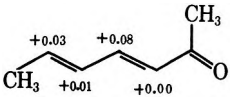
Nmr chemical shifts should be particularly characteristic of the electronic structure of the dienones. For example, **15** exists exclusively as an *s-trans*-enone; yet H_4, though no longer deshielded by an *s-cis*-carbonyl, appears far downfield at τ 3.08. This suggests that for *trans,trans*-dienones carbonyl anisotropic effects on chemical shifts are small with respect to charge distribution effects. The deshielding of H_4 can be rationalized in terms of contributions of structures such as **6a** to the dienone resonance hybrid. Both resonance



6a **6b**

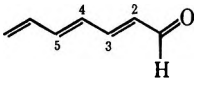
theory and HMO theory predict the alternation of charge along the diene chain which seems to be reflected in the relative chemical shifts of H_3, H_4, and H_5 for cyclic dienones[4,37b] and our compounds. For both types of dienones H_6 has about the same chemical shift as H_5 in apparent contradiction to the expected electron deficiency at C_6. However, hydrogens on the termini of dienes probably are intrinsically more shielded than the internal olefinic hydrogens. *trans,trans*-2,4-Hexadiene in CCl_4 exhibits multiplets at τ 4.4 and 4.05 for the terminal (2,5) hydrogens and internal (3,4) hydrogens, respectively. Using these as standard values for an "unperturbed" diene and treating H_{3-5} as internal hydrogens and H_{6c} as a terminal hydrogen, we have calculated Δτ values for **6** which represent the downfield shifts experienced by the olefinic hydrogens owing to conjugation of the diene with a carbonyl group.[40] Sorensen's equation (3), developed for polyenylic cations,[41] can then be used to compute a rough estimate of the "excess positive charge density" at each carbon (Δ*q*). The calculation assumes that carbonyl anisotropic effects are relatively small and that the olefinic carbons of *trans,trans*-2,4-hexadiene bear no net charge. The results in formula **54** show the expected charge alternation. CNDO/2 calculations of Bertelli and

$$\Delta q = 14.7\Delta\tau \qquad (3)$$



54

Andrews[42] on *all-s-trans*-2,4,6-heptatrienal (**55**) over carbons 2–5 in the same sense though excess negative



55

charge at C_2 and C_4 is predicted.[43] The calculated charges on the hydrogen atoms themselves, however, show a totally different pattern with excess positive charge decreasing in the order 2 > 4 > 5 > 3.[42]

The nmr data, as a whole, point clearly to planar or nearly planar conjugated dienones and agree in all details with deductions based on infrared spectroscopy. Further, the nmr data require that the diene units have s-trans conformations and that 6*c*-phenyl groups be twisted out of the diene plane.

Ultraviolet Spectra.—Wavelength maxima and intensities for π,π* absorptions of the dienones are recorded in Table I. The π,π* assignment is clear from the intensity of these absorptions and the bathochromic shift of the maxima caused by an increase in solvent polarity.[44] Data for n,π* absorptions are collected in Table III. Assignment of these bands is based on their characteristic low intensities and the hypsochromic shift of the absorption maximum for **6** as solvent polarity is increased.[45a]

The uv data are in good qualitative accord with conformational deductions based on infrared and nmr spectroscopy. The π,π* maxima of all-trans aliphatic dienones **6**, **9**, **13**, **15**, and **17** in cyclohexane range from 265 to 278 nm (ε 27,000–33,500) in good agreement with data on analogous rigid steroidal dienones[46] which must be nearly planar. *trans,trans*-Dienones with *s-cis*-enone moieties exhibit reduced π,π* absorption intensities as would be expected on the basis of enone

(36) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 21–22.

(37) (a) A. A. Bothner-By and R. K. Harris, *J. Amer. Chem. Soc.*, **87**, 3445, 3451 (1965); (b) A. A. Bothner-By and E. Moser, *ibid.*, **90**, 2347 (1968).

(38) This is true in the specific case of conjugated cyclohexadienones as well.[4, 37b]

(39) See ref 25 for a discussion of this effect.

(40) For H_{s-5} $\Delta\tau_i = 4.05 - \tau_{H_i}$ (dienone), and $\Delta\tau_{6c} = 4.4 - \tau_{6c}$ (dienone).

(41) T. S. Sorensen, *J. Amer. Chem. Soc.*, **87**, 5075 (1965).

(42) D. J. Bertelli and T. G. Andrews, Jr., *ibid.*, **91**, 5280 (1969).

(43) The trienal is chosen for comparison rather than the more closely related *trans*-2,4-pentadienal, because the latter lacks a terminal substituent which seems to play an important role in affecting the calculated charge on the carbons of the terminal double bond. Compare the compounds above and methyl vinyl ketone with 3-penten-2-one in ref 41.

(44) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1964, p 207.

(45) Reference 44: (a) pp 186–187; (b) p 389.

(46) $\Delta^{3,5}$-7-ones give $\lambda_{max}^{EtOH\ or\ CHCl_3}$ 277–280 (24,400–28,000) and $\Delta^{4,6}$-3-ones give $\lambda_{max}^{EtOH\ or\ Et_2O}$ 273–284 (26,300–33,900). *Cf.* ref 17, pp 407–409. Roughly 11 nm must be subtracted from the ethanol values to allow direct comparison with our cyclohexane values.

TABLE III
n,π* ABSORPTION MAXIMA FOR DIENONES

Compound	λ_{max}	ϵ_{max}	Solvent
trans-2,4-Pentadienal	325	51	95% EtOH[a]
6	335	65	C_6H_{12}
	330	84	Et_2O
	b		MeOH
7	330	90	Et_2O
8	335	82	Et_2O
15	320	93	Et_2O
17	320	126	Et_2O
	343	57	
	358	48	
	377	29	
18	338	63	Et_2O

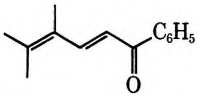
[a] E. L. Pippen and M. Nanaka, *J. Org. Chem.*, **23**, 1580 (1958). [b] Not observable.

data.[6,17] Thus ϵ_{max} values for **11** and **20** are 22,800 and 22,000–25,000, respectively.

Comparison of cinnamylideneacetone (**22**) with its *s-cis*-4-methyl derivative **25** reveals a drop in ϵ_{max} from 38,000 to 30,800, and the trienones **41** and **42** are related in a similar fashion. In every case the shift of the enone conformational equilibrium to all-s-cis is accompanied by a bathochromic shift of λ_{max} which is in accord with planar s-cis conformations. A change in structure from trans,trans to α,β-cis reduces the intensity of the π,π^* absorption as expected[6,17] and is accompanied by a bathochromic shift of up to 13.5 nm (**22** *vs.* **23**). This shift, like the infrared and nmr data, is in accord with conformations which do not deviate significantly from planarity.

Isomerization of *all-trans*-dienones which bear a phenyl substituent in the 6*t* position to the γ,δ-cis compounds is accompanied by large hypsochromic shifts and reduction of π,π^* absorption intensity (**24**, **26**, **30**). These shifts confirm that 6c phenyl groups are twisted out of conjugation as deduced by nmr spectroscopy. The case of γ,δ-cis aliphatic dienones is not so clear. Trans → cis isomerization of the γ,δ double bond (**6** → **8**, **13** → **14**, and **17** → **18**) is accompanied by a bathochromic shift of the π,π^* maximum (**8** and **14** exhibit two maxima of similar intensity) and a pronounced diminution of absorption intensity. Use of the $\epsilon^\theta/\epsilon^0 = \cos^2\theta$ relationship,[47] where θ is the angle of deviation from planarity about an essential single bond, gives values for of 28, 37, and 36° for **8**, **14**, and **18**, respectively. However, sterically induced nonplanarity does not offer an entirely consistent explanation of these spectral changes. Normally a hypsochromic shift of the absorption maximum accompanies twisting about an essential single bond,[45b] not the bathochromic shift seen here. If the twisting is the result of steric interaction between the 6c-methyl and the 4 substituent, it ought to be much more pronounced in **18**, where it is the result of a 1,3 methyl–methylene interaction, than it is in **8** and **14**, where it is the result of a 1,3 methyl–hydrogen interaction.[23] Yet this does not appear to be the case (*vide supra*). The vicinal coupling constant across the essential single bond of the diene unit in **8** is 10.5 Hz, seemingly inconsistent with the large distortion[37b] from planarity estimated from absorption intensities. Finally, **9** with a 6c-methyl group has "normal" π,π^* absorption intensity. Thus, the source of the low absorption intensities in the γ,δ-cis compounds is not completely clear, and it seems probable that **8** and **14** do not deviate from planarity by an angle so large as that derived from the Braude equation.[47]

The highly substituted dienone **16** should have no stable planar conformation for its diene unit.[48] In fact, Dreux, *et al.*, have suggested that it is nonplanar on the basis of its weak uv absorption, λ_{max}^{EtOH} 286 nm (ϵ 16,200).[49] Our glpc purified **16** exhibits an even lower value, $\epsilon_{max}^{C_6H_{12}}$ 10,000, which supports the nonplanar structure. β-Ionone (**36**) is almost certainly nonplanar as well.[48] Duperrier and Dreux[49b] also suggest that dienone **56b** is nonplanar on the basis of its λ_{max}^{EtOH} 301 nm but give no value for ϵ_{max}. The low



56b

absorption intensities for the highly substituted α,β-*cis*-dienones **37**–**40** (compare **23**) also suggest nonplanar structures.

Allinger, *et al.*,[50] have calculated ultraviolet spectra for *all-s-trans*-dienones in the vapor phase. They obtain two π,π^* maxima with a 6–35-nm separation but report that the plotted spectra exhibit only one merged maximum. The vapor-phase spectrum of **6** exhibits two maxima of nearly equal intensity at 253 and 244 nm with hints of other structure in the form of inflections on either sides of the main absorption. While these may be the two maxima predicted by Allinger, *et al.*,[50] their *ca.* 1500-cm^{-1} separation also allows interpretation in terms of vibrational structure. They could also arise as a consequence of coexisting *s-cis*- and *s-trans*-enone conformers exhibiting different maxima. The calculations predict that very similar 5–6-nm bathochromic shifts will be caused by α-, β-, γ-, or δ-methyl substitution. Our data for 3,5-heptadienone (**6**) and its monomethyl derivatives reveal 4-, 7.5-, 2.5-, and 13-nm bathochromic shifts for α-, β-, γ-, and δ-methyl substitution, respectively (*cf.* **6**, **15**, **11**, **13**, and **9**). The large shift associated with β substitution may arise from the preference for the *s-cis*-enone conformation. The large δ-methyl effect is supported by the 20-nm shift caused by introducing a δ-methyl into **31** (compare **32**) and is not predicted by the calculations.[51] Agreement between the calculated and observed maxima for the few compounds for which data exist (**6**, **9**, and **19**) is poor.

Conformation of Phenone Derivatives.—Deduction of conformation is a more subtle problem in the case of the phenone derivatives **31**–**34** than it is for the other dienones. All the phenone derivatives exhibit a single carbonyl stretching frequency in the infrared suggesting conformational homogeneity. For structures

(47) H. B. Klevens and J. R. Platt, *J. Amer. Chem. Soc.*, **71**, 1714 (1949); E. A. Braude and F. Sondheimer, *J. Chem. Soc.*, 3754 (1955).

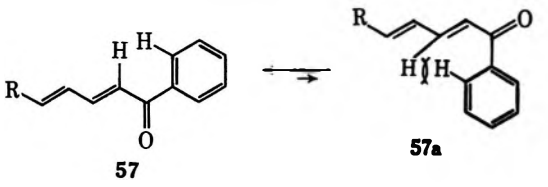
(48) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).

(49) (a) P. Roullier, D. Gagnaire, and J. Dreux, *Bull. Soc. Chim. Fr.*, 168 (1966); (b) A. Duperrier and J. Dreux, *Tetrahedron Lett.*, 3127 (1970).

(50) N. L. Allinger, T. W. Stuart, and J. C. Tai, *J. Amer. Chem. Soc.*, **90**, 2809 (1968).

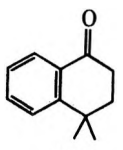
(51) The observed pattern of substituent effects is also not consistent with changes in π-electron density only during the $\pi \rightarrow \pi^*$ transition which can be obtained from Salem's π change densities for 3,5-hexadienone (**19**): A. Devaquet and L. Salem, *ibid.*, **91**, 3793 (1969).

which approach planarity the s-cis conformation (**57**) should be preferred owing to steric destabilization of



57 **57a**

the s-trans conformation (**57a**). Compound **58**, a rigid *s-trans*-phenone, exhibits $\nu_{CO}/(CCl_4)$ 1688 cm^{-1}.[52]

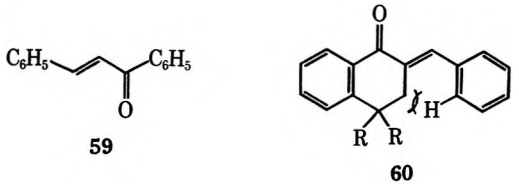


58

Substraction of 8 cm^{-1} to simulate the effect of a second conjugated double bond[19] gives a value of 1660 cm^{-1} for an s-trans model. The crotonylidene derivatives **31–33** do exhibit carbonyl stretching at higher frequencies, 1665–1670 cm^{-1}, in agreement with s-cis conformations, but the difference is small. No deduction can be drawn from comparison of **34** and **35**.

Nmr evidence is more compelling. For aliphatic dienones the chemical shift of H_3 is conformation dependent varying from τ 4.30 and 4.2 for rigid s-trans compounds **17** and **18** to *ca.* τ 3.9 for **11** which is entirely s-cis. In **31–33** H_3 appears much farther downfield and over the small range of τ 3.18–3.29. Using τ 3.9 and 4.25 as base values for H_3 in s-cis and s-trans conformers, respectively, we have estimated the chemical shift of H_3 in **31–33** by introducing corrections for the inductive effect of β-phenyl *vs.* β-methyl and for the long-range anisotropic effect of the phenyl group.[53] The values τ 3.9 for s-trans and τ 3.3 for s-cis show that the s-cis conformation is in much closer agreement with the average observed value of τ 3.23. A consequence of the s-cis conformational preference should be a downfield shift of the H_4 signal owing to anisotropy of the carbonyl group. Such a shift of 0.2–0.25 ppm occurs on going from aliphatic dienones to phenone derivatives (**6** and **13** *vs.* **31** and **33**). This is also true when a 6c-methyl is present (**8**, **9**, and **14** *vs.* **32**).

Comparison of the uv absorption of **34** and its s-cis analog **35** reveals a decrease in absorption intensity in the latter. Hassner and Cromwell[54] interpreted a similar, but more pronounced, difference between *trans*-chalcone (**59**) and two s-cis analogs (**60**) in terms of an



59 **60**

a, R = H
b, R = CH_3

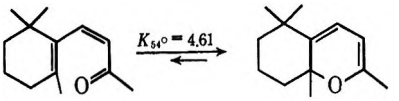
(52) We thank Mr. Michael McLaughlin for the gift of a sample of this compound.

(53) Details are given in the Experimental Section.

(54) (a) A. Hassner and N. H. Cromwell, *J. Amer. Chem. Soc.*, **80**, 893 (1958). (b) In the solid state chalcone and its *p*-methoxy derivative are s-cis: D. Rabinovitch and G. M. J. Schmidt, *J. Chem. Soc. B*, 6, 11 (1970).

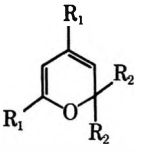
s-trans conformation for **59**. We feel that a significant portion of the low absorption intensities of **35**, **60a**, and **60b** can be attributed to nonplanarity arising from 1,3 hydrogen–methylene and phenyl–methylene interactions.[23] The reduced intensity of the uv absorption of *cis*-1-phenylpropene relative to that of its trans isomer[55] illustrates the operation of just such an effect. It is worth noting that the carbonyl stretching frequencies reported for **59**, **60a**, and **60b** in CCl_4, 1667, 1666, and 1673 cm^{-1}, respectively,[54] do not support a change in enone conformation.

Dienone–Pyran Equilibria.—α,β-*cis*-Dienones can also exist as valence isomeric α-pyrans. The only reported example of a compound which exists as an equilibrium mixture is *cis*-β-ionone (**61**).[56] Intercon-



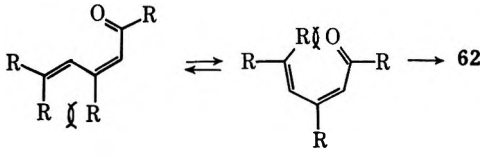
61a **61b**

version of **61a** and **61b** is so facile as to prevent their separation. 2,2,4,6-Tetraalkyl-α-pyrans (**62**) have been prepared by treatment of α-pyrones with 2 equiv of a Grignard reagent and appear to exist exclusively in the pyran form.[57] Thus, the compounds do not form 2,4-dinitrophenylhydrazone derivatives; their uv spectra are similar to those of *s-cis*-dienes;[58] and catalytic hydrogenation of **62b**[59] gives a tetrahydropyran. In



62a, $R_1 = R_2 = CH_3$
b, $R_1 = CH_3$; $R_2 = n$-Bu

contrast, the aliphatic α,β-*cis*-dienones **7**, **10**, **12**, **21**, and **53**, which do not have the above substitution pattern, exist in the dienone form. Evidence for this is their intense uv absorption and the presence of an nmr signal for the uniquely deshielded H_5. These compounds can all adopt stable planar dienone conformations (see Table I). Owing to steric interactions *cis*-β-ionone (**61a**) and the 4,6,6-trialkyldienones corresponding to general structure **62** have no available stable planar



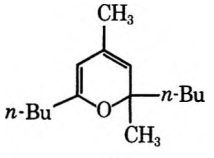
(55) C. G. Overberger, D. Tanner, and E. M. Pearce, *J. Amer. Chem. Soc.*, **80**, 4566 (1958): *cis*-1-Phenylpropene, λ_{max} 242 (13,000) and 280 (320); trans-, λ_{max} 249 (17,000) and 283 (1000) (no solvent given).

(56) E. N. Marvell, G. Caple, T. A. Gosink, and G. Zimmer, *ibid.*, **88**, 619 (1966).

(57) R. Gompper and O. Christman, *Chem. Ber.*, **94**, 1784 (1961).

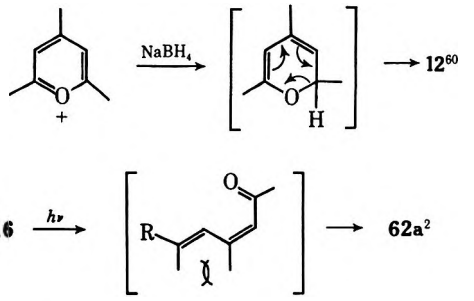
(58) For **61b** λ_{max} (CH_3OH) 208 (3230) and 253 (7000).

(59) The method of synthesis and structural evidence[57] are also consistent with a mixture of **61b** and i.

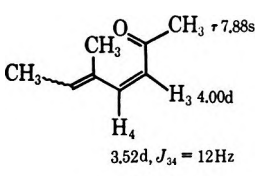


i

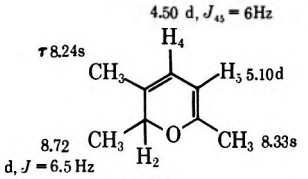
conformations and therefore prefer their pyran forms (**61b** and **62**). Because interconversion is rapid the method of synthesis does not determine the valence isomer obtained. Thus



It is steric destabilization of the dienone valence isomer, not the specific 4,6,6-trisubstitution pattern, which is essential for the existence of pyran. Thus, irradiation of **13** produces **14** and a second fraction which has been identified as an equilibrium mixture of **63a** and **63b**.[2,61] Compounds **63** were isolated as a single



63a



63b

glpc fraction which exhibited uv maxima at 284 nm (ε 3900) and 211 nm (ε 2300). The nmr spectrum in $CDCl_3$ (see **63b**) was consistent with the pyran structure and in agreement with other α-pyran spectra reported in the literature.[56,62,63] In addition weaker signals corresponding to nonintergral numbers of hydrogens were observed and assigned as shown in **63a**. Comparison of the integral of the dienone H_3, H_4, and H_6 (assumed to occur near H_3 and H_4) signals with that of all other olefinic hydrogens leads to an estimate of 13% dienone content. In agreement with the argument above, 2,3,4,6-tetramethyl-α-pyran contains no dienone valence isomer (benzene solution)[63] while simple dienals do not close to pyrans.[64]

Replacement of a 6-alkyl group with a substituent capable of extending the conjugated π system understandably leads to greater preference for the open dienone valence isomer. Thus Köbrich and Wunder[65] have shown that the highly hindered 4,6-dimethyl-6-phenyldienone **38** exists primarily as a dienone and that this is probably also the case when the conjugating 6 substituent is *p*-anisyl (**39**), *p*-(dimethylamino)phenyl (**40**), and *trans*-β-styryl (**45**). Whether a significant amount of the pyran valence isomer is present in these cases is under investigation.

Dreux and his coworkers have studied pyrans under conditions which place them in equilibrium with *trans*-dienones and have recently observed that many of the same factors pointed out above control the α-pyran ⇄ *trans*-dienone equilibrium.[49b]

Summary.—Analysis of ir, uv, and nmr data has led to a set of self-consistent deductions about the conformations of conjugated dienones. Except for highly substituted compounds which are nonplanar or tautomerize to α-pyrans, evidence is in favor of conformations which are close enough to planarity to be labeled meaningfully as s-cis or s-trans. Deviations from planarity of less than 25°, however, will not be revealed by our data.

Experimental Section

General and Spectra.—Infrared spectra of CCl_4 solutions or thin films were recorded on a Beckman IR-10 instrument and were calibrated with the 1601-cm^{-1} polystyrene band. Absolute positions of absorption maxima are estimated to be accurate within ±5 cm^{-1}, and relative positions of any two carbonyl maxima can be estimated within ±3 cm^{-1}. Nmr samples were prepared as *ca.* 10% solutions in carbon tetrachloride. Spectra were recorded at a probe temperature of 39 ± 2° and were calibrated relative to internal tetramethylsilane. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by the University of Massachusetts Microanalytical Laboratory directed by Mr. Charles Meade. Compound **35** was prepared as reported in the literature,[66] mp 137–139° (lit.[66] 132–134°). Condensation of *O*-nitrocinnamaldehyde and acetyl methyl diethyl phosphonate anion gave **28**, mp 73–74° (lit.[67] 73.5°).

Perdeuteriomalonic Acid (49). From Carbon Suboxide.—Approximately 3 g of carbon suboxide[68] was obtained from 84 g of diacetyltartaric anhydride. The carbon suboxide was contained in a vacuum trap in a Dry Ice–acetone bath. To the trap were added 15 ml of dry tetrahydrofuran and 4 ml of D_2O. The trap was sealed and left in an ice bath for 20 hr. The tetrahydrofuran was removed on a rotary evaporator. The trap was then attached to a vacuum pump to remove the remaining volatiles. There remained in the flask 1.85 g of perdeuteriomalonic acid as white crystals.

Exchange Method.—Malonic acid (11 g, 0.105 mol) and 3 g of D_2O (0.15 mol) were added to a 300-ml, round-bottom flask. The mixture was allowed to stand for 30 min. The water was then removed on a vacuum pump (0.05 mm). This procedure was repeated five times. The isotopic purity of the product was not assayed.

trans,trans-**Sorbic-2,4-d_2 Acid (50).**—To a 200-ml, round-bottom flask equipped with a reflux condenser were added 6.315 g of perdeuteriomalonic acid (58.5 mmol), 4.1 g of crotonaldehyde (58.5 mmol), and 10 ml of anhydrous pyridine. The flask was set in an oil bath at 80–85°. Gas evolution was monitored with a mineral oil bubbler. The flask was removed from the oil bath after 3 hr. The contents of the flask as transferred to a 50-ml erlenmeyer flask and cooled in an ice bath. An ice-cold solution of 3 ml of concentrated sulfuric acid in 6 ml of water was added to the flask. The precipitate was collected by filtration. The filtrate was cooled in an ice bath, and an additional crop of crystals was collected. The precipitate was dissolved in 50 ml of boiling water. The flask was left at 5° in a cold room overnight. Subsequent filtration and drying gave 1.442 g of sorbic-*2-d* acid (21.8%) as long white needles, mp 133–134° (reported[69] for perprotio compound, mp 134°). In a second run a yield of 31.4% was obtained. The isotopic purity was not assayed.

trans,trans-**3,5-Heptadienone-*3,5-d_2*** (6-*3,5-d_2*).—To a 100-ml, three-neck, round-bottom flask equipped with nitrogen inlet tube, reflux condenser, magnetic stirring bar, and a rubber stopple were added 1.442 g of sorbic-*2-d* acid (12.7 mmol) and 50 ml of dry ether. A 2.3 *M* solution of methyllithium in ether (12.6 ml, 25.3 mmol) was added with a syringe. A precipitate formed upon the addition of the methyllithium, and this precipitate did

(60) A. T. Balaban, G. Mihai, and C. D. Nenitzescu, *Tetrahedron*, **18**, 257 (1962).

(61) Experimental details are given in ref 2.

(62) A. Hinnen and J. Dreux, *C. R. Acad. Sci.*, **255**, 1747 (1952).

(63) J. Royer and J. Dreux, *Tetrahedron Lett.*, 5589 (1968).

(64) S. Sarel and J. Rivlin, *Israel J. Chem.*, **1**, 221 (1963); *Tetrahedron Lett.*, 821 (1965); J. C. Anderson, D. G. Lindsay, and C. B. Reese, *Tetrahedron*, **20**, 2091 (1964).

(65) G. Köbrich and D. Wunder, *Justus Liebigs Ann. Chem.*, **654**, 131 (1962).

(66) W. Herzog and J. Kreidel, *Chem. Ber.*, **55**, 3394 (1922).

(67) L. Diehl and A. Einhorn, *ibid.*, **18**, 2327 (1885).

(68) C. D. Hurd and F. D. Pilgrim, *J. Amer. Chem. Soc.*, **55**, 757 (1933).

(69) C. F. H. Allen and J. Van Allan, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 783.

not disappear after complete addition. The contents of the flask were heated at reflux for 30 min. Water (10 ml) was added slowly at first, then rapidly. The mixture was transferred to a separatory funnel and shaken, and the aqueous layer was discarded. The ether layer was washed with three additional 10-ml portions of water. The ether layer was dried for 1 hr (Na_2SO_4). Subsequent filtration and removal of the ether on a rotary evaporator at reduced pressure left a yellow oil. This oil was filtered through 20 g of alumina with 35 ml of benzene. Removal of the solvent on a rotary evaporator left 0.7135 g of *all-trans*-3,5-heptadienone-*3,5-d*$_2$ as a yellow oil (50.7%). Further purification was effected by distillation on a micromolecular still at 45–50° (30 mm). A sample of the product was analyzed by glpc, and it had the same retention time as the perprotio compound (on a 20 ft × 0.25 in. 5% FFAP on Anakrom AB column): ir (CCl_4) 2230 (C—D), 1685, 1667 (C=O), 1630, 1594, 1582 (C=C), 972 cm^{-1} (trans CH=CH).

trans,trans-**5-Phenyl-2,4-pentadienoic-*2-d* Acid (52).**—To a 100-ml, round-bottom flask were added 2.80 g of *trans*-cinnamalmalonic acid, 25 ml of anhydrous tetrahydrofuran, 1 ml of D_2O, and one drop of a 2.58 *M* solution of methyllithium in ether. The liquid was evaporated under a stream of nitrogen. The flask was placed for 2 hr on a rotary evaporator attached to a vacuum pump (0.05 mm). This exchange procedure, without the addition of methyllithium, was repeated two additional times to give *trans*-cinnamylidenemalonic acid-*O,O-d*$_2$ (51).

The flask was then fitted with a reflux condenser leading to a mineral oil bubbler. To the flask were added 20 ml of anhydrous pyridine and two drops of D_2O. The contents of the flask were heated at reflux for 3 hr, then allowed to cool to room temperature, and poured into 200 ml of ether. The ether solution was extracted with three 50-ml portions of 6 *N* hydrochloric acid. The ether layer was then shaken with 100 ml of 5% potassium hydroxide solution and was discarded. The aqueous layer was washed with 50 ml of ether, separated, and acidified with concentrated hydrochloric acid. The resulting suspension was extracted with two 50-ml portions of ether. The combined ether layers were dried for 1 hr (Na_2SO_4). Subsequent decantation and removal of ether on a rotary evaporator at reduced pressure left a yellow solid. This solid was taken into 200 ml of hot benzene, and the solution was added to a 200-ml, round-bottom flask equipped with a reflux condenser and containing 0.2 g of iodine. The contents of the flask as heated at reflux and irradiated with a 250-W sun lamp for 30 min. The benzene was removed on a steam bath. The remaining solid was washed with two 30-ml portions of a saturated potassium iodide solution and was collected on a Büchner funnel. The collected solid was recrystallized five times from 25-ml portions of benzene to yield 0.672 g of *trans,trans*-5-phenyl-2,4-pentadienoic-*2-d* acid as off-white plates, mp 167.5–170°. The reported melting point of the perprotio compound is 165–166°.[70] The combined mother liquors from the benzene recrystallizations were shaken with three 30-ml portions of a saturated solution of potassium iodide. The benzene was removed on a steam bath, and the residue was recrystallized from 20 ml of benzene to give an additional 0.435 g of product. The total yield was 1.307 g (58%). The application of this same decarboxylation procedure to perprotiocinnamalmalonic acid resulted in a 46% yield of *trans,trans*-5-phenyl-2,4-pentadienoic acid, mp 169–170°.

trans,trans-**6-Phenyl-3,5-hexadienone-*3-d* (22-*3-d*).**—*trans,trans*-5-Phenyl-2,4-pentadienoic-*2d* acid was treated with 2 equiv of methyllithium in diethyl ether using a procedure identical with that described for preparation of 6-*3,5-d*$_2$ (*vide supra*). The product was obtained as white crystals: mp 68–68.5°; ir (CCl_4) 2250 (C—D), 975, 967 cm^{-1} (trans CH=CH).

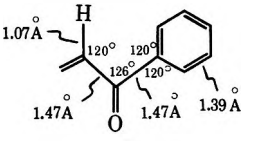
all-trans-**3,5,7-Nonatrienone (41).**—*all-trans*-2,4,6-Octatrienoic acid[71] (2.24 g, 16.2 mmol) was treated with 2 equiv of methyllithium in diethyl ether using the procedure described for preparation of 6-*3,5-d*$_2$ (*vide supra*) to give 0.87 g (39%) of a yellow oil: ir (CCl_4) 992 cm^{-1} (trans CH=CH); uv max (C_6H_{12}) 310 nm (ϵ 27,000), 299 (27,300) (lit.; Table II); nmr (CCl_4) τ 8.22 (d, 3, J = 5 Hz, CH_3CH=), 7.85 (s, 3, CH_3CO–), 4.3–3.4 (complex, 5, olefin hydrogens), 2.94 (q, 1, $J_{4,3}$ = 16 Hz, $J_{4,5}$ = 10 Hz, 4-hydrogen).

(*E,E,E*)-**4-Methyl-3,5,7-nonatrienone (42).**—(*E,E,E*)-3-Methyl-2,4,6-octatrienoic acid[72] was prepared by the method described by Kuhn and Hoffer[73] for the high-melting isomer, giving white needles, mp 164–165° (lit.[73] mp 160–161°). This acid (1.85 g, 12.2 mmol) was treated with 2 equiv of methyllithium using the procedure described for preparation of 6-*3,5-d*$_2$ (*vide supra*) to give 1.38 g (75%) of a yellow oil: ir (CCl_4) 978, 957 cm^{-1} (trans CH=CH); nmr (CCl_4) τ 8.20 (d, 3, J = Hz, CH_3CH=), 7.82 (s, 3, CH_3CO), 7.75 (s, 3, 4-methyl), 4.5–3.1 (complex, 5, olefin hydrogens).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.38; O, 10.65. Found: C, 80.01; H, 9.45.

all-trans-**1-Phenyl-2,4,6-octatrienone (44).**—To a 250-ml, red-tinted, round-bottom flask equipped with a reflux condenser and containing a few boiling stones were added 6 g (15.8 mmol) of benzoylmethylenetriphenylphosphorane, 5 g of sorbaldehyde, and 70 ml of dry benzene. The solution was heated at reflux for 24 hr. The benzene was removed on a rotary evaporator at reduced pressure leaving a slushy, brown solid which was then washed with three 25-ml portions of ether. The remaining solid (triphenylphosphine oxide) was discarded. The ether was removed on a rotary evaporator at reduced pressure leaving a brown solid. This solid was washed with three 50-ml portions of hot Skellysolve B. The combined washings were cooled in an ice bath, and the resulting precipitate was collected by filtration. This gave 1.8 g of an orange-yellow powder, which upon sublimation (100°, 1 mm) gave 1.5 g of yellow crystals, mp 88–94°. The sublimate was filtered through 50 g of alumina with approximately 100 ml of benzene–Skellysolve B (1:1). Solvent was removed on a steam bath, and the resulting solid was recrystallized from two 30-ml portions of Skellysolve B to give 0.4 (12.6%) of *all-trans*-1-phenyl-2,4,6-octatrienone, mp 97–97.5° (lit.[74] mp 94–95°), ir (CCl_4) 1000 cm^{-1} (trans CH=CH).

Estimation of the Chemical Shift of H_3 in Phenone Derivatives.—The estimation was made for planar s-cis and s-trans conformers by starting with chemical shifts for H_3 in pure *s-cis*- (11) and *s-trans*- (17 and 18) methyl dienones. These values were corrected for the effect of replacing the methyl group with an "in-plane" phenyl group. Long-range phenyl anisotropic effects were estimated from Jackman and Sternhell's version of the Bovey–Johnson shielding diagram.[75a] The distance between H_3 and the center of the benzene ring was estimated on the basis of the following parameters.[76] The distance was 4.0 Å



in the s-cis conformer and 4.9 Å in the s-trans conformer. The inductive effect of β-phenyl *vs.* β-methyl was estimated starting with the chemical shift difference between the methyl groups of propane and ethylbenzene, 0.3 ppm.[75] This value must be reduced by the deshielding which the methyl of ethylbenzene experiences from phenyl anisotropy since we have estimated this separately. Reference to the Bovey–Johnson diagram[75a] suggests that this effect should be *ca.* 0.2 ppm. Therefore the inductive effect of β-phenyl should cause a *ca.* 0.1 ppm downfield shift of H_3. Calculations are summarized below.

	τ(s-trans)	τ(s-cis)
Base value for CH_3 derivative	4.25	3.9
Inductive effect of β-phenyl	−0.1	−0.1
Anistropic effect of phenyl	−0.25	−0.5
Chemical shift of H_3 in phenyl derivative	3.9	3.3

Registry No.—**6**, 18402-90-9; 6-*3,5-d*$_2$, 29178-91-4; **7**, 4857-17-4; **8**, 4173-40-4; **9**, 16647-04-4; **10**, 29178-96-9; **11**, 29178-97-0; **12**, 29178-98-1; **13**, 29178-99-2; **14**, 29179-00-8; **15**, 29179-01-9; **16**, 29179-02-0; **17**, 29179:03-1; **18**, 29179-04-2; **19**, 20432-46-6; **20**, 29179-11-1; **21**, 29179-12-2; **22**, 29179-13-3; **22-*3-d***,

(70) C. Liebermann, *Chem. Ber.*, **28**, 1438 (1895).

(71) R. Kuhn and M. Hoffer, *ibid.*, **63**, 2169 (1930).

(72) For nomenclature see J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968).

(73) R. Kuhn and M. Hoffer, *Chem. Ber.*, **65**, 651 (1932).

(74) R. Kuhn and H. A. Staab, *ibid.*, **87**, 262 (1954).

(75) (a) Reference 15, p 95; (b) ref 15, p 164.

(76) L. E. Sutton, Ed., "Tables of Interatomic Distances and Configurations in Molecules and Ions," Supplement, Special Publication No. 18, The Chemical Society, London, 1965.

29179-14-4; **23**, 29179-15-5; **24**, 29246-55-7; **25**, 29179-16-6; **26**, 29179-17-7; **27**, 29179-18-8; **28**, 29179-19-9; **29**, 29179-20-2; **30**, 29179-21-3; **31**, 29179-22-4; **32**, 29179-23-5; **33**, 29179-24-6; **34**, 29179-25-7; **35**, 29179-26-8; **36**, 79-77-6; **37**, 29179-27-9; **38**, 29179-28-0; **39**, 29179-29-1; **40**, 29179-30-4; **41**, 16326-91-3; **42**, 29179-32-6; **43**, 29179-33-7; **44**, 29179-34-8; **45**, 29179-35-9.

Acknowledgments. We thank Professor Kenneth L. Williamson of Mt. Holyoke College for running a 100-MHz nmr spectrum and decoupling experiments on compound **6** and Mr. William Nason for running several infrared and ultraviolet spectra. The nmr spectrometer used in this work was purchased with funds from a research instruments grant of the National Science Foundation.

Photoisomerization Products of Conjugated Dienones

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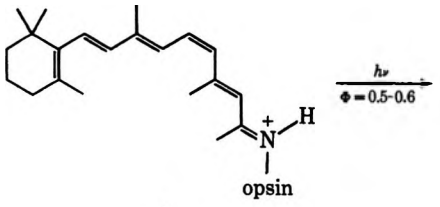
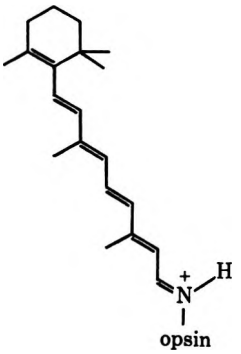
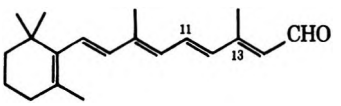
Irradiation of dilute (10^{-2}–10^{-4} *M*) diethyl ether solutions of conjugated dienones rapidly produces photostationary-state mixtures of the all-trans, cis,trans, and trans,cis isomers. Exceptions are 4-methyl-3,5-heptadienone (**21**), which undergoes isomerization only about its α,β double bond, and the 1-aryldienones **44**, **46**, and **47**, which seem to undergo only γ,δ photoisomerization. α-Pyran formation occurred on irradiation of 4,6-dimethyl-3,5-heptadienone (**24**) and 5-methyl-3,5-heptadienone (**27**) as the result of ring closure of the respective α,β-*cis*-dienones in what are possibly dark reactions. Failure to detect any cis,cis photoisomers has been tentatively attributed to their rapid conversion to α,β-cis-γ,δ-trans isomers *via* the valence isomeric α-pyrans in the dark.

The initial chemical event in vision is a remarkably specific cis to trans photoisomerization of the 11 double bond of the visual pigment rhodopsin (**1**).[2] This isomerization, which triggers but does not constitute in itself the visual process, occurs in an 11-*cis*-retinal unit which is bound to the protein opsin *via* a protonated Schiff base linkage and fits snugly into the protein surface. The specificity of 11 isomerization could be an electronic property of the protonated retinylidene imine chromophore or might arise because alternative isomerizations are geometrically prohibited by the fit with the protein surface. Photoisomerization of *all-trans*-retinal itself (**2**) has been variously reported to give a mixture of isomers in which all-trans predominates[3] and to give the 13-cis isomer specifically.[4,4a] In a program designed to investigate the properties of excited states which are electronically similar to those of rhodopsin and retinal, we have examined the relatively simple dienones which have two isomerizable double bonds and a carbonyl group in conjugation.



1





2

In contrast to the extensive studies of cross-conjugated dienones,[5] investigations of the photochemistry of conjugated dienones have been relatively rare. Early reports showed that conjugated dienones bearing aromatic groups gave photodimers both in solution and solid phases.[6,7] Irradiation of some steroidal dienones resulted in formation of cyclobutane-type dimers.[8] *trans*-β-Ionone (**3**) gave pyran **4**[9–11] and smaller amounts of the unconjugated dienone **5**.[12] In an

(1) (a) NSF Cooperative Fellow, 1965–1969; (b) Alfred P. Sloan Foundation Fellow, 1969–1971.

(2) For a summary of knowledge of the molecular basis of vision, see E. W. Abrahamson and S. E. Ostroy, *Progr. Biophys. Mol. Biol.*, **17**, 179 (1967); C. B. D. Bridges, *Compr. Biochem.*, **27**, 31 (1967); G. Wald, *Science* **162**, 230 (1968).

(3) R. Hubbard, R. I. Gregerman, and G. Wald, *J. Gen. Physiol.*, **36**, 415 (1953); G. Wald, P. K. Brown, and R. Hubbard, *Proc. Nat. Acad. Sci. U. S.*, **41**, 438 (1953); P. K. Brown and G. Wald, *J. Biol. Chem.*, **222**, 865 (1956).

(4) M. Mousseron-Canet, *Advan. Photochem.*, **4**, 219 (1966).

(4a) NOTE ADDED IN PROOF.—For a recent quantitative study involving four photoisomers of retinal, see A. Kropf and R. Hubbard, *Photochem. Photobiol.*, **12**, 249 (1970).

(5) *Cf.* K. Schaffner, *Advan. Photochem.*, **4**, 81 (1966).

(6) (a) H. Stobbe and C. Rücker, *Chem. Ber.*, **44**, 869 (1911); (b) H. Stobbe, A. Hensel, and W. Simon, *J. Prakt. Chem.*, **110**, 129 (1925).

(7) A more recent study has confirmed dimer formation but has resulted in revision of some noncyclobutane structures proposed earlier (see ref 46): D. J. Zepka, Ph.D. Thesis, University of Massachusetts, 1969.

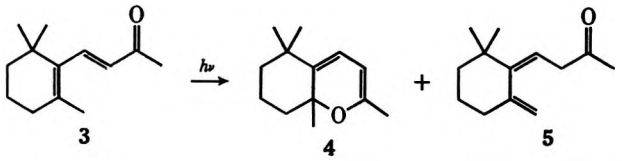
(8) H. C. Thorndsen, G. Cianelli, D. Arigoni, and O. Jeger, *Helv. Chim. Acta*, **45**, 2342 (1962); M. B. Rubin, D. Glover, and R. G. Parker, *J. Org. Chem.*, **29**, 68 (1964); *Tetrahedron Lett.*, 1075 (1964); and A. Devaquet and L. Salem, *J. Amer. Chem. Soc.*, **91**, 3793 (1969).

(9) G. Büchi and N. C. Yang, *Chem. Ind. (London)*, 355 (1955); *J. Amer. Chem. Soc.*, **79**, 2318 (1957).

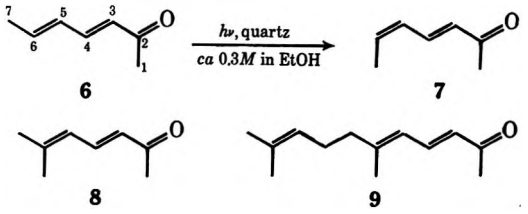
(10) Pyran **4** is in thermal equilibrium with a small amount of the valence isomeric dienone.[9]

(11) E. N. Marvell, G. Caple, T. A. Gosink, and G. Zimmer, *ibid.*, **88**, 619 (1966).

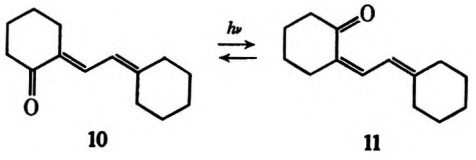
(12) P. de Mayo, J. B. Stothers, and R. W. Yip, *Can. J. Chem.*, **39**, 2135 (1961).



attempt to develop a general pyran synthesis, Büchi and Yang irradiated several other aliphatic dienones (6–9).[9] Compound 6 gave a photoisomer to which



they assigned structure 7 plus polymer, while 8 and 9 were reported to give only polymer. One example of a clean geometrical photoisomerization, that of 10, has been reported.[13]



Results

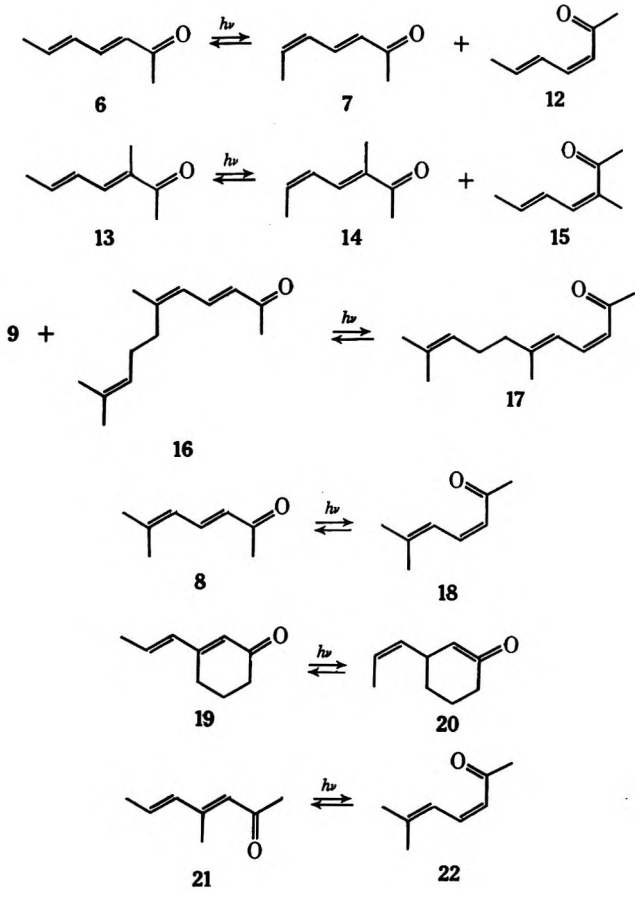
We chose to study the conjugated dienones as 10^{-2} to 10^{-4} M solutions in diethyl ether. The volatile diethyl ether did not interfere with glpc analysis and showed no propensity to react with dienones under irradiation. In these solutions geometrical isomerization is much more efficient than bimolecular reactions such as dimer and polymer formation. Typically irradiation led rapidly to photostationary-state mixtures of all the possible geometrical isomers except cis,cis. Under our conditions (*e.g.*, relatively short irradiation times) no other monomeric photoproducts such as unconjugated dienones or photoreduction products could be detected.

A thorough study of conjugated dienones was undertaken using infrared, nmr, and uv spectroscopy; and correlations between spectra and molecular structure are reported in the preceding paper.[14] Structures of new compounds are based on these data except where noted.[15] Most analytical and preparative separations were accomplished using glpc, and here also useful general correlations between structure and physical properties emerged. For a given aliphatic dienone, retention times increased in the order cis,trans[16] < trans,cis < all-trans, the last two isomers being closely spaced. For δ-phenyldienones the order of elution of cis,trans and trans,cis isomers was reversed.

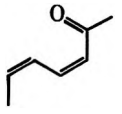
Aliphatic Dienones.—Photoisomerizations of aliphatic dienones are shown in Chart I. Irradiation of 6,

CHART I

PHOTOISOMERIZATION OF ALIPHATIC DIENONES IN Et_2O



which is typical, gave a photostationary-state mixture (see Table I) of 6, 7, and 12. The glpc purified isomers exhibited spectral properties uniquely consistent with these structures.[18] No evidence was found for the presence of the cis,cis isomer (23) in the photolysate.



Extended irradiation of a 10^{-2} M solution of 6 in diethyl ether at 254 nm to give a photostationary-state mixture caused loss of only 12% of the total dienone to a nonvolatile fraction. Photoisomerization of dienones 8 and 19 proceeded in a similar fashion, the products being identified spectroscopically.[14] 3-Methyl-3,5-heptadienone (13) rapidly gave two photoisomers whose glpc elution pattern paralleled that of the 3,5-heptadienone isomers 7 and 12. They were assigned the (*E*,*Z*) and (*Z*,*E*) structures 14 and 15, respectively, on this basis alone. Only one photoisomer could be detected from irradiation of 21 under glpc conditions which resolve 6 and 7. The infrared, uv, and nmr spectra of this material were identical with those of the authentic (*Z*,*E*) isomer (22) prepared by sodium

(13) I. T. Harrison and B. Lythgoe, *J. Chem. Soc.*, 837 (1958).

(14) A. F. Kluge and C. P. Lillya, *J. Org. Chem.*, **36**, 1977 (1971).

(15) Structures of starting trans,trans isomers are known from previous work in many cases. Nevertheless, we have in every case made a thorough spectroscopic study to prove their stereochemistry.[14]

(16) The configuration of the double bond nearest the carbonyl group is specified first. When the terms cis and trans are ambiguous the isomers will be labeled (*E*,*E*) and (*E*,*Z*), etc.[17]

(17) J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968).

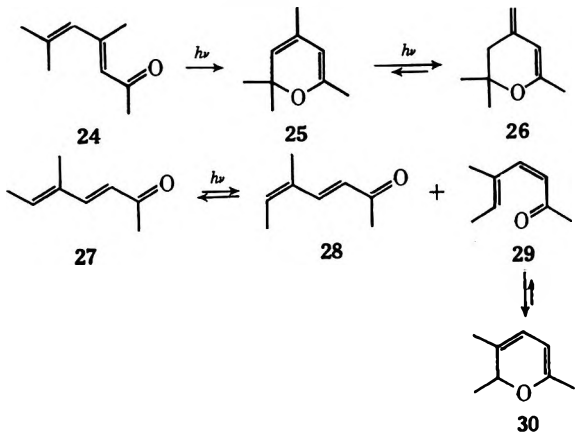
(18) Büchi and Yang[9] reported isolation of 7 by irradiation of 6 and subsequent distillation of the photolysate. We find, however, that 6 and 7 are so similar in volatility that a 30-ft glpc column is necessary for their separation. The uv absorption reported by Büchi and Yang for their "7" is virtually identical with that of our isomer 12,[14] and, owing to its high volatility, 12 could have been separated from a crude photolysate by distillation. Thus Büchi and Yang's photoproduct is the α,β-cis isomer 12.

borohydride reduction of 2,4,6-trimethylpyrilium perchlorate.[19] Owing to separation difficulties, a mixture of the (*E*,*E*) and (*E*,*Z*) isomers of pseudoionone **9** and **16**, respectively, was irradiated. The structure of the third isomer which appeared at a shorter glpc retention time was assigned tentatively on the basis of the nmr spectrum of partially purified photolysate (see Experimental Section).

Two aliphatic dienones gave α-pyrans upon irradiation (Chart II). Irradiation of (*E*)-4,6-dimethyl-3,5-

CHART II

PYRAN FORMATION

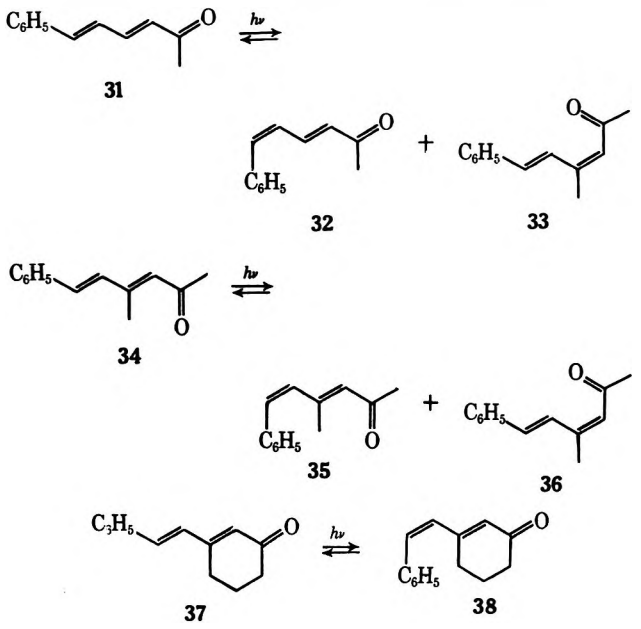


heptadienone (**24**) gave a fraction with a much shorter glpc retention time. Under proper conditions this peak could be partially resolved showing that at least two photoproducts were present; however, separation under preparative conditions was not possible. These photoproducts were shown to be **25** and **26** by comparison of an nmr spectrum of a mixture with published values for **25** and **26**.[20] Further, an authentic mixture produced by treatment of 2,4-6-trimethylpyrone with methylmagnesium chloride[21] exhibited nmr and glpc properties which were identical save for a minor variation attributable to a difference in isomer ratio. Disappearance of **24** was first order to at least 84% reaction,[22] and at long irradiation times **24** is completely consumed. Therefore conversion of **24** to **25** is not reversible under our conditions. The longer the irradiation time is the higher the ratio of **26** to **25**; so **26** probably arises from **25** in a second photoreaction. Irradiation of **27** resulted in rapid production of two components with shorter glpc retention times, and continued irradiation gave a photostationary state. The first eluted component was shown to be an equilibrium mixture of 87% α-pyran **30** and 13% its dienone valence isomer **29**.[14] The second eluted component was assigned the (*E*,*Z*) structure **28**.[14]

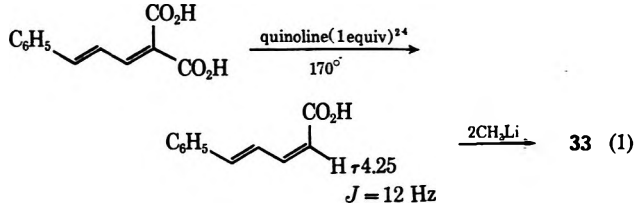
δ-Phenyldienones.—Black light[23] irradiation of δ-phenyldienones causes isomerizations similar to those observed for most aliphatic dienones (Chart III).

CHART III

PHOTOISOMERIZATION OF δ-PHENYLDIENONES IN Et_2O



Three isomers of 6-phenyl-3,5-hexadienone (**31**, **32**, and **33**) are formed. The cis,trans isomer (**33**) was identical in all respects with material prepared as shown in eq 1.



(*E*,*E*)-4-Methyl-6-phenyl-3,5-hexadienone (**34**) gave **35** and **36**. The latter gave mixtures of **34** and **36** on glpc collection because of the high temperature required for separation. Thus, its structure was proven by independent synthesis as shown in Scheme I. A separation of the potassium salts was achieved in the hydrolysis stage. The α,β-cis (*Z*) configuration of acid **42** was revealed by the long-range deshielding of H_γ (τ 1.5, doublet, J = 16 Hz) by the carboxyl carbonyl.[14,25] The glpc retention time of synthetic **36** was identical with that of the second eluted photoisomer, and irradiation of **36** in ethyl ether gave the same photostationary-state mixture produced from **34**. Spectral properties of **36** are entirely consistent with its assigned structure.[25a]

1-Phenyldienones.—Irradiation of crotonylideneacetophenone (**44**) and two related dienones resulted in geometric isomerization that was apparently specific for the γ,δ double bond. Our work in this series was not extended to isolation and characterization of the photoisomers because of difficulty in achieving glpc

(19) A. T. Balaban, G. Makai, and C. D. Nenitzescu, *Tetrahedron*, **18**, 257 (1962).

(20) A. Hinnen and J. Dreux, *C. R. Acad. Sci.*, **255**, 1747 (1962).

(21) R. Gompper and O. Christmann, *Chem. Ber.*, **94**, 1784 (1961). These authors assigned structure **25** to the product but Hinnen and Dreux[20] showed that it was a mixture of **25** and **26**.

(22) This experiment was performed under conditions in which there was a large excess of light and most photons were not absorbed by dienone.

(23) A broad spectrum of wavelengths between 300 and 400 nm with a maximum intensity at 366 nm.

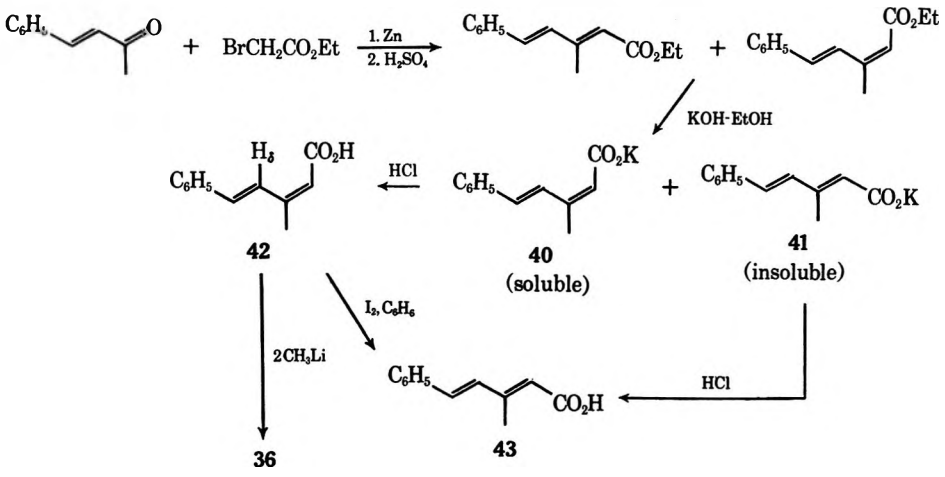
(24) C. Liebermann, *Chem. Ber.*, **28**, 1438 (1895).

(25) See G. Englert, *Z. Anal. Chem.*, **181**, 447 (1961), for a similar effect in dienoic esters.

(25a) NOTE ADDED IN PROOF.—We have recently detected a second photoproduct as a shoulder on the leading edge of the glpc peak of the all-trans isomer. Thus failure to observe α,β isomerization in phenone derivatives may be only the result of inadequate analytical methods: R. A. Gaudiara, unpublished work.

SCHEME I

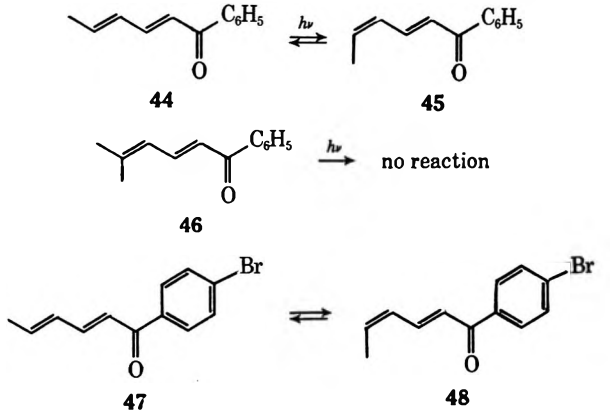
PREPARATION OF (*Z,E*)-4-METHYL-6-PHENYL-3,5-HEXADIENONE (36)



separations. The photoreactions are shown in Chart IV. Irradiation of **44** gave a photoisomer of shorter

CHART IV

PHOTOISOMERIZATION OF 1-PHENYLDIENONES IN Et_2O

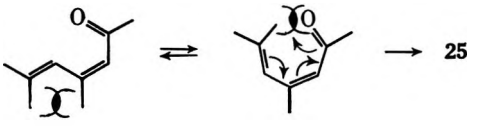


glpc retention time. The percentage of this isomer in the photostationary-state mixture was estimated from the partially resolved glpc peaks as 30 to 40%. The uv spectrum of the photostationary-state mixture shows a 3-nm bathochromic shift from λ_{max} of **44** with 95% of the original absorption intensity. Assuming that λ_{max} for **44** and its photoisomer are coincident and that 40% photoisomer is present, we estimate the absorption intensity of the photoisomer as 88% of that of **44**.[26] This estimate and the near-identity of the glpc retention times for **44** and the photoisomer are in accord with a γ,δ-cis structure (**45**) for the photoisomer. Irradiation of **46** gave no photoisomers as judged by glpc analysis. This is in accord with the idea that **44** undergoes only γ,δ isomerization, since in the case of **46** γ,δ isomerization is degenerate. 1-(*p*-Bromophenyl)-2,4-hexadienone (**47**) gave an isomer which is tentatively assigned as **48** (see Experimental Section).

Discussion

These results show that geometric isomerization is the primary mode of photoreaction for conjugated dienones. Excellent material balance at the photostationary states shows that polymerization does not compete effectively, and analysis of the volatile products shows that the reactions are clean photoisomerizations. Several potentially meaningful generalizations can be drawn from the data. In no case did we succeed in detecting a *cis,cis*-dienone among the photoproducts. However, the aliphatic and the δ-phenyldienones gave all of the other possible geometric isomers. The sole exception to this is **21** which does not undergo γ,δ isomerization. In contrast, 1-phenyldienones appear to undergo γ,δ isomerization exclusively.

Two dienones, **24** and **27**, appear unusual in that they give pyrans on irradiation. In fact, the photoisomerization of these dienones is entirely normal. α-Pyrans exist only in cases where their valence isomeric α,β-*cis*-dienones possess no stable planar conformations.[14] Thus, irradiation of **24** almost certainly gives the sterically destabilized dienone **49**. Closure of **49** to



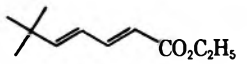
give pyran **25** is the inexorable consequence of thermodynamics. Irradiation of **27** gives a (*Z,E*) isomer that is in thermal equilibrium with the valence isomeric pyran **30**.[14] Whether closure to pyrans is light-catalyzed under our conditions cannot be deduced. Marvell, *et al.*, have shown that dark interconversion of *cis*-β-ionone and its corresponding α-pyran is sufficiently rapid to account for our observations.[11] Formation of the methylenetetrahydropyran **26** from **25** can be formulated as a photochemical [1,3] sigmatropic shift of hydrogen for which the suprafacial pathway is allowed.[27]

One of the most striking aspects of our data is the complete absence of *cis,cis*-dienones from the photolysates. Isomerization of cis,cis isomers during glpc analysis could be the cause. However, the crude photolysates exhibited no significant nmr or ir absorption which could not be accounted for on the basis of the isolated isomers. Furthermore in the case of 6-phenyl-

(26) The fact that the first condition is not quite met means that we will tend to underestimate the absorption intensity of the photoproduct.

(27) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, p 122.

3,5-hexadienones (**31–33**) a semicarbazone mixture prepared directly from the crude photolysate was resolved into only three components by tlc. This could be a consequence of nonformation of cis,cis isomers. However, we can think of no obvious reason for this. In the closely related isomerization of the dienonic ester **50**, evidence for four geometric isomers has been ob-

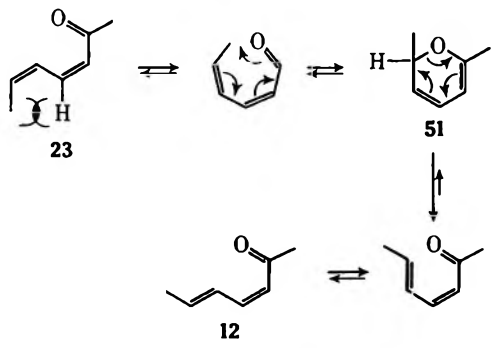


50

tained.[28] Owing to their predictably low uv absorption intensities,[14] cis,cis isomers would be expected to be major components of the photostationary states. Alternatively, the absence of cis,cis isomers can be interpreted in terms of their rapid disappearance *via* dark reactions. Facile interconversion of α,β-*cis*-dienones and α-pyrans could afford such a pathway. Scheme II shows that *cis,cis*- and *cis,trans*-dienones

SCHEME II

EQUILIBRATION OF *cis,cis*- AND *cis,trans*-DIENONES



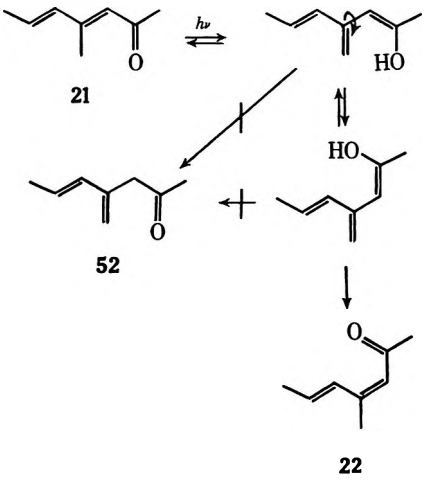
could be equilibrated *via* the α-pyran **51** which is valence isomeric to both. A ΔF° value of -1.8 kcal/mol for conversion of **23** to **12** would correspond to *ca.* 5% **23** at equilibrium near room temperature, an amount undetectable by our ir and nmr analyses.[29] 1,3 methyl–hydrogen interactions similar to that in **23** have been estimated as 1.6 kcal/mol.[30]

Only tentative explanations can be advanced to account for lack of γ,δ isomerization of 4-methyl-3,5-heptadienone (**21**). Owing to steric destabilization of the s-trans conformer (**21a**), this compound exists exclusively as an *s-cis*-enone (**21**).[14] Except for **8**,

which cannot undergo γ,δ isomerization, **21** is unique among our aliphatic dienones in this regard. Compounds **13** and **19**, which have conformationally homogeneous *s-trans*-enone units,[14] undergo normal isomerization. Should the unique conformation of **21** lead to rapid photoenolization to the exclusion of normal photoisomerization, exclusive α,β isomerization could be explained as shown in Scheme III. However, for simple enones geometric isomerization is faster than

SCHEME III

PHOTOENOLIZATION OF 4-METHYL-3,5-HEPTADIENONE



photoenolization.[28,31] Furthermore, no unconjugated products (*e.g.*, **52**), which are characteristic of enone photoenolization, were detected. Alternatively, lack of γ,δ isomerization could be a property peculiar to s-cis excited states. The other aliphatic dienones could undergo γ,δ isomerization *via* s-trans excited states populated by Franck–Condon excitation of s-trans ground-state conformers. Different reactivity of the s-cis and s-trans excited states of dienes has been recognized for some time,[32] and similar behavior has been suggested in the case of enones.[33] Neither of the above proposals provides an obvious basis for explaining the lack of isomerization specificity for 4-methyl-6-phenyl-3,5-hexadienone (**34**) which also has a conformationally homogeneous *s-cis*-enone unit.

Work on the mechanism of photoisomerization of 3,5-heptadienones (**6**, **7**, and **12**) has revealed moderately efficient isomer interconversion $\Phi = 0.12$–0.36 and has demonstrated that a common excited state is not involved.[34] We are conducting further experiments designed to clarify the role of cis,cis isomers and to test for photoenolization and for conformational dependence of photoreactivity.

Experimental Section

General.—Glpc analysis was performed using an F & M Model 609 instrument with a flame ionization detector, with 0.25-in. columns. Analytical columns were AC-1 copper, 6 ft, 30% DC-200 on 60–80 mesh Chromosorb W; AC-2 copper, 10 ft, 10% FFAP on 60–80 mesh Chromosorb W; and AC-3 copper, 20 ft, 5% FFAP on 60–80 mesh Anakrom AB. A Varian Aerograph Autoprep A-700 glpc unit was used for preparative work. The following $^3/_8$-in.-diameter preparative columns were employed: PC-1 aluminum, 20 ft, 30% SE-30 on 60–80 mesh Chromosorb W; PC-2 aluminum, 10 ft, 25% DC-200 on 60–80 mesh Chromosorb W; PC-3 aluminum, 20 ft, 30% FFAP on 60–80 mesh Chromosorb W; PC-4 aluminum, 20 ft, 30% QF-1 on 60–80 mesh Chromosorb W; and PC-5 copper, 30 ft, 0.25-in. diameter, 25% FFAP on 60–70 mesh Anakrom AB.

For analytical irradiations a stoppered 1-cm path length fused silica uv cuvette was placed flush with the window of an ultraviolet hand lamp. This lamp, a Black-Ray Model X4 obtained

(28) M. J. Jorgenson, *J. Amer. Chem. Soc.*, **91**, 6432 (1969); see Experimental Section, p 6443.

(29) At the temperature of glpc analysis, 100–110° interconversion could easily be too rapid to allow resolution.[11]

(30) J. Packer, J. Vaughan, and E. Wong, *ibid.*, **80**, 905 (1958).

(31) M. J. Jorgenson and N. C. Yang, *ibid.*, **85**, 1698 (1963); N. C. Yang and M. J. Jorgenson, *Tetrahedron Lett.*, 1203 (1964).

(32) R. S. H. Liu, N. J. Turro, Jr., and G. S. Hammond, *J. Amer. Chem. Soc.*, **87**, 3406 (1965).

(33) R. A. Schneider and J. Meinwald, *ibid.*, **89**, 2023 (1967).

(34) A. F. Kluge and C. P. Lillya, *ibid.*, **92**, 4480 (1970), and paper in press.

from Scientific Glass Apparatus Co., Inc., Bloomfield, N. J., emitted a broad spectrum λ 300–400 nm with a maximum intensity at 366 nm (black light). Preparative irradiations were performed with either a Hanovia immersion apparatus employing a 450-W medium-pressure mercury arc (679A-36) and Corex filter sleeve or with a Rayonet photochemical reactor equipped with 16 RPR 3500A or RPR 2537A lamps. Solutions irradiated in the Rayonet reactor were contained in an 800-ml quartz vessel equipped with a reflux condsnser. Deaeration had no observable effect on the reactions.

Elemental analyses were performed by the University of Massachusetts Microanalytical Laboratory directed by Mr. Charles Meade. Spectrophotometric equipment and infrared, uv, and nmr spectral data are described in detail in the preceding paper[14] and are not reproduced here.

Photostationary-State Compositions.—Dilute solutions of the dienones in ether were irradiated until their compositions no longer changed. Analysis was performed using glpc by injecting the ether solutions directly into the chromatograph. Light sources are 300–400 (see hand lamp above), "2537" Rayonet RPP-2537A lamps whose main output is at 253.7 nm but also emits energy at 313 and 366 nm; 313 and 254 nm refer to monochromatic light of the designated wavelength obtained by passing the output of a medium-pressure mercury arc through a series of filter solutions and plates.[35] The results are presented in Table I.

TABLE I
PHOTOSTATIONARY-STATE COMPOSITIONS IN DIETHYL ETHER

		% composition		
Compd[a]	Light source	All-trans or (*E*,*E*)	Trans,cis or (*E*,*Z*)	Cis,trans or (*Z*,*E*)
6	300–400	49.1	25.2	25.7
	"2537"	32.6	20.7	46.7
	313	48.0	30.0	22.0
	254	28.4	20.4	51.2
8	300–400	74.8		25.2
	"2537"	47.4		52.6
	254	46.6		53.4
9	300–400	46	31	23
13	300–400	41.5 ± 3	19 ± 3	39.5 ± 3
19	300–400	55.8	44.2	
21	300–400	51.2		48.8
27	300–400	19 ± 3	13 ± 3	68 ± 3[b]
31	300–400	40[c]	50[c]	10[c]
34	300–400	37[c]	27[c]	36[c]
37	300–400	36[d]	64[d]	

[a] The all-trans or (*E*,*E*) compound. [b] Exists as 13% dienone and 87% α-pyran. [c] Values approximate owing to incomplete resolution of (*E*,*E*) and (*E*,*Z*) isomers and isomerization during glpc analysis. [d] Values approximate owing to isomerization during glpc analysis.

Preparation of Dienones from Dienoic Acids.—The Tegnér reaction[36] was found to be a generally efficient and completely stereospecific method of preparing methyldienones from their corresponding dienoic acids. To a three-neck, round-bottom flask equipped with reflux condenser, nitrogen inlet, magnetic stirring bar, and rubber stopple were added from 2 to 20 mmol of dienoic acid and from 40 to 300 ml of ether. The system was purged with nitrogen and 2 equiv of another solution of methyllithium was added with a syringe. The solution was heated at reflux for 30 min, then cooled. Water (20–50 ml) was added and the layers were separated. The ether layer was separated, washed with additional water, and dried (Na_2SO_4). Removal of solvent gave the crude dienone, containing small amounts of alcohol impurity. The crude dienone was filtered through activated alumina (3–20 g) with a suitable solvent such as hexane or benzene. Removal of solvent gave the alcohol-free dienone which could be obtained in very pure form by micromolecular distillation or sublimation.

Irradiation of *all-trans*-3,5-Heptadienone (6).—Compound **6** was prepared according to the method of Attenburrow, *et al.*[37] Material prepared according to this procedure contained approximately 15% of the trans,cis isomer **7**. The two isomers were separated using PC-5 at 130°. It was found that the best method for the preparation of isomerically pure **6** was through treatment of *all-trans*-sorbic acid with methyllithium (*vide supra*) which gave **6** in 75% yield. Analysis by glpc (AC-3,110°) showed less than 0.1% of **7** as the only impurity. Five irradiations were performed in an Hanovia apparatus using approximately 0.3 g of **6** in 600 ml of ether (*ca.* 5×10^{-3} *M*). Each solution was irradiated for 12 min at which time glpc analysis revealed three components: **12** (T_r[38] 14.4 min, 27%), **7** (T_r 18.4 min, 27%), and **6** (T_r 19.2 min, 46%). Solvent was removed by careful distillation, and the cis,trans isomer **12** was isolated by glpc as a light yellow oil using PC-1 at 120°. The trans,cis isomer **7** was isolated using PC-5 at 130°.

It was found that **12** could be prepared in greater quantities by irradiation in the Rayonet reactor. A solution of 2.5 g of **6** (containing 15% of **7**) in 500 ml of ether (4.55×10^{-2} *M*) was irradiated with RPR 2537A lamps. After 4 hr the photomixture contained approximately 40% **12**. The loss of monomer to polymer at this concentration was still small.

Irradiation of *trans*-6-Methyl-3,5-heptadienone (8).—The procedures of Kuhn and Hoffer[39] and Fischer and Lowenberg[40] were followed for the preparation of **8**. The reaction product was purified in each case by preparative glpc (PC-1, 150°). A solution of 0.0842 g of **8** in 500 ml of ether (1.36×10^{-3} *M*) was irradiated in a Rayonet reactor equipped with RPR 3500A lamps. Analytical glpc (AC-1, 110°) showed two components: **18** (T_r 16.4 min) and **8** (T_r 24 min). The irradiation was terminated after 20 min, at which time the percentage composition of **8** was *ca.* 25%. Two similar irradiations were run, and solvent was carefully removed from each mixture. The *cis* isomer **18** was isolated by preparative glpc as a light yellow oil using PC-1 at 150°. Isomer **18** could be prepared in greater quantity by irradiation with RPR 2537A lamps. A solution of 2.5 g of **8** in 600 ml of ether (3.36×10^{-2} *M*) when irradiated for 6 hr gave a mixture that was approximately 50% **18**. Losses to polymerization were small.

Irradiation of *trans*-3-Propenyl-2-cyclohexenone (19).—The procedure of Crison and Normant was used to prepare **19**.[41] An ether solution 2.46×10^{-2} *M* in **19** was irradiated in a 1-cm path length with a uv hand lamp, and the reaction was followed by glpc (AC-2, 140°). At zero time there was a single component, **19** (T_r 36 min). As the irradiation progressed, a new isomer **20** (T_r 24.4 min) appeared and in 20 min built up to a stationary concentration of 44%. In a preparative run 1.34 g of **19** in 500 ml of ether (1.98×10^{-2} *M*) was irradiated for 1 hr in a Rayonet reactor equipped with RPR-3500A lamps. The isomer mixture was approximately 40% **20**. The solvent was removed leaving a yellow oil. Cis isomer **20** was isolated by preparative glpc using PC-1 at 180°. In contrast to **19** it exhibits only weak ir absorption in the 980-cm^{-1} region.

Irradiation of (*E*,*E*)-4-Methyl-3,5-heptadienone (21).—Compound **21** was prepared in 81.7% yield through treatment of (*E*,*E*)-3-methyl-2,4-hexadienoic acid[39] with methyllithium. The 2,4-dinitrophenylhydrazone derivative melted at 172–173° (cor) (lit.[41] 172°). Compound **21** was further purified by preparative glpc using PC-3 at 130° to give a clear oil. A cyclohexane solution 3.62×10^{-3} *M* in **21** was placed in a 1-cm path length uv cuvette and was irradiated with a uv hand lamp. Analysis by glpc (AC-2, 100°) showed starting material (T_r 26.8 min) and a new isomer, **22** (T_r 22.4 min). At 56 min a photostationary state consisting of only these two isomers was reached. In a preparative run a solution of 0.5 g of **21** in 500 ml of ether (8.07×10^{-3} *M*) was irradiated for 1 hr with RPR 3500A lamps. Glpc showed the isomer mixture was 40% **22**. After the volume of this solution was reduced to *ca.* 4 ml, the (*Z*,*E*) isomer **22** was isolated by preparative glpc using PC-3 at 130°. This material exhibited ir, nmr, and uv absorption as well as a glpc retention time that was identical with that of authentic (*Z*,*E*)-4-methyl-3,5-heptadienone (**22**).[19]

Irradiation of Pseudoionone.—Pseudoionone was prepared according to the "Organic Syntheses" procedure.[42] Further

(35) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," Wiley, New York, N. Y., 1966, pp 728–747.

(36) C. Tegnér, *Acta Chem. Scand.*, **6**, 782 (1952).

(37) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(38) Glpc retention time.

(39) R. Kuhn and M. Hoffer, *Chem. Ber.*, **65**, 651 (1932).

(40) F. G. Fischer and K. Lowenberg, *Justus Liebigs Ann. Chem.*, **494**, 279 (1932).

(41) C. Crison and H. Normant, *Bull. Soc. Chem. Fr.*, 1451 (1957).

(42) A. Russell and R. L. Kenyon, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1951, p 747.

purification was effected by preparative glpc using PC-1 at 190°. Pseudoionone prepared by this procedure is a mixture of two isomers (derived from geranial and neral which together constitute citral). The first eluted isomer constituted approximately one-third of the isomer mixture. The nmr spectra of the two isomers are very similar. The uv max (C_6H_{12}) for both isomers was 283 nm. The ϵ_{max} for the isomer of shorter retention time was 18,200 and that for the other was 18,900. On the basis of the uv spectra and the glpc retention times (γ,δ-cis isomers have shorter retention times than all-trans isomers), the isomer of shorter retention time is assigned (*E,Z*) stereochemistry (16), and the other isomer is assigned (*E,E*) stereochemistry (9). A solution of 0.0031 g of pseudoionone (mixture of 9 and 16) in 4 ml of ether (4×10^{-3} *M*) was added to a 1-cm path length uv cuvette, and the solution was irradiated with a uv hand lamp.

Analysis by glpc (AC-1, 160°) showed, in addition to 16 (T_r 30.8 min) and 9 (T_r 38 min), a new component, 17 (T_r 27.6 min). The isomerization was slow compared to other systems. In a preparative run, 0.41 g of pseudoionone in 500 ml of ether (4.27×10^{-3} *M*) was irradiated for 23 hr in a Rayonet reactor equipped with RPR 3500A lamps. Solvent was removed to give a yellow oil. Analysis by tlc (silica gel, $CHCl_3$) showed three spots very near starting material (R_f 0.5), one minor spot at R_f 0.75, and several spots near the application point. The three components of R_f 0.5 were separated from the rest of the reaction mixture by preparative tlc using two 20 × 20 cm plates coated with an 0.5-mm layer of uv-indicating silica gel. The plates were developed twice with $CHCl_3$ and were visualized by uv. A band from 5 to 15 cm along the plates was scraped off. The removed silica gel was shaken with 100 ml of $CHCl_3$ and the slurry was filtered by suction. Solvent was removed leaving 0.3 g of a yellow oil. Analysis by glpc showed the following isomer composition: **9**, 46%; **16**, 31%; **17**, 23%. The base line was irregular leading up to the first peak (17) suggesting decomposition. The nmr spectrum of the isomer mixture exhibited a new signal at τ 3.37 (J = 12 Hz) which was assigned to H_4 of the (*Z,E*) isomer (**17**). Integration of this signal gives an estimate of **17** as 26 ± 4% (glpc estimate 23%).

Irradiation of (*E,E*)-3-Methyl-3,5-heptadienone (13).—Compound **16** was prepared by treating (*E,E*)-2-methyl-2,4-hexadienoic acid[43] with methyllithium (*vide supra*) and was isolated in 51% yield as a clear oil. Spectral properties are tabulated in the preceding paper and are in full accord with structure **13**.

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.40; H, 9.70.

An ether solution 1×10^{-3} *M* in **13** was placed in a 1-cm path length uv cuvette and was irradiated with a uv hand lamp to give a photostationary state after 1 hr. Analysis by glpc (AC-3, 130°) showed **13** (T_r 9.5 min) at zero time. As the irradiation progressed two new isomers appeared at T_r 6.6 and 8.5 min. These isomers are respectively assigned (*Z,E*) and (*E,Z*) stereochemistry by analogy of their retention times with those of **6**, **7** and **12** on the same column.

Irradiation of (*E*)-4,6-Dimethyl-3,5-heptadienone (24).—Dienone **24** was prepared in 47% yield by treatment of (*E*)-3,5-dimethyl-2,4-hexadienoic acid[44] with methyllithium (*vide supra*). The resulting clear oil gave a 2,4-dinitrophenylhydrazone derivative, mp 149–150° (lit.[41] mp 148°).

Irradiation of a 4.93×10^{-3} *M* methanol solution of **24** in a uv cuvette was followed by glpc (AC-1,110°). In addition to **24** (T_r 38.2 min) a new peak (T_r 12 min) appeared and after 46 min accounted for 84% of the total area under the two peaks. A plot of log [**24**] *vs.* time for this reaction gave a straight line. In a preparative run 0.5 g of **24** in 500 ml of ether (7.25×10^{-3} *M* was irradiated for 2 hr with RPR 3500A lamps. Glpc showed conversion of **24** to product was essentially complete. After removal of the solvent the photoproduct was collected by preparative glpc (PC-4,100°). This product exhibited glpc retention times (AC-1 and AC-2) and nmr absorptions which were identical with those of an authentic mixture of **25** and **26**.[21] In our hands **25** and **26** exhibited identical glpc retention times and the amount of **26** was determined to be 45% by nmr integration. A second run made under the same conditions but irradiated for only 90 min gave only 90% conversion of starting dienone, and the photoproducts contained only 25 ± 2% **26**.

Irradiation of (*E,E*)-5-Methyl-3,5-heptadienone (27).—A 3.4 × 10^{-3} *M* ether solution of **27**, prepared according to Dautwitz,[45] was irradiated in a uv cuvette, and progress of the reaction was monitored by glpc (AC-2). Elution at 75° gave a single peak (**29** and **30**) after which the column temperature was increased to 130° (9°/min) causing elution of **28** and **27** in that order. The photostationary state was reached after 94 min. In a preparative run 2.40 g of **27** in 500 ml of ether (3.87×10^{-2} *M*) was deaerated by bubbling nitrogen through the solution for 30 min. The solution was maintained under an atmosphere of nitrogen while it was irradiated with RPR 3500A lamps for 9 hr. Removal of solvent left a yellow oil which was separated into its components by preparative glpc (PC-4,140°). The second eluted component was identified as the (*E,Z*) isomer **28** while the first eluted component was a mixture of **29** and **30**:[14] ir (film) 1695 (sh), 1666, 1622, 1042 cm^{-1}; nmr (see ref 14); uv max (C_6H_{12}) 284 nm (ϵ 3920), 211 nm (ϵ 2320). The mixture of **29** and **30** was air sensitive and elemental analysis had to be performed immediately on glpc purified material which was further purified by molecular distillation.

Anal. Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.30; H, 9.70.

The semicarbazone had mp 165–166° dec.

Anal. Calcd for $C_9H_{15}N_3O$: C, 59.65; H, 8.34; N, 23.18. Found: C, 59.60; H, 8.27; N, 23.00.

Irradiation of *all-trans*-6-Phenyl-3,5-hexadienone (31).—Compound **31** was prepared by the procedure of Plati, *et al.*[46] The light yellow crystals, mp 66.5–67°, could be obtained in colorless form by sublimation (0.05 mm, 50°), which left the melting point unchanged. A solution of 0.05 g of **31** in ether was irradiated with RPR 3500A lamps for 4 hr. The photostationary state was reached sometime after 2 hr. Ten more runs were made under identical conditions with an irradiation time of 20 min which gave a composition of 35% **32**, 5% **33**, and 60% **31**. The combined products were dissolved in the minimum amount of methanol and separated by preparative glpc (PC-1,200°). The first eluted compound was **32**, the trans,cis isomer, a yellow oil. The cis,trans isomer **33** was eluted next; however, collected samples were contaminated with **31** owing to isomerization of the column or detector block.

Irradiation of *cis,trans*-6-Phenyl-3,5-hexadienone (33).—Compound **33** was obtained as a yellow paste in 93% yield by treatment of *cis,trans*-5-phenyl-2,4-pentadienoic acid[24] with methyllithium (*vide supra*). When analyzed by glpc (AC-1, 175°) a neat sample showed 92% **33** and 8% **31**, while a 10^{-3} *M* ether solution showed 23% **33** and 77% **31**. Irradiation of a 1.16×10^{-3} *M* solution of **33** with RPR 3500A lamps for 2 hr gave the same photostationary-state isomer mixture produced by irradiation of **31**.

Synthesis of (*E,E*)-3-Methyl-5-phenyl-2,4-pentadienoic Acid (43) and (*Z,E*)-3-Methyl-5-phenyl-2,4-pentadienoic Acid (42).—A mixture of ethyl esters (51 g) prepared according to Kuhn and Hoffer[39] was hydrolyzed in a solution of 20 g of potassium hydroxide in 40 ml of water and 300 ml of ethanol. The potassium salt of the (*E,E*) acid (**41**) was collected by filtration from the cooled hydrolysate. Reprecipitation from 200 ml of hot water by addition of concentrated hydrochloric acid and subsequent recrystallization from benzene gave 14.5 g of **43** as white crystals: mp 163–163.5° (lit.[39] 160°). The basic filtrate was diluted with 700 ml of water, treated with decolorizing charcoal, filtered, and acidified with concentrated hydrochloric acid. The resulting precipitate was collected and dried. Reprecipitation from 100 ml of hot benzene by addition of 500 ml of pentane gave 8.4 g of the (*Z,E*) acid (**42**) as white crystals: mp 157°; nmr (acetone) τ 4.17 (s, broad, 1, H_2), 2.93 (d, 1, J_{45} = 16 Hz, H_6), 1.50 (d, 1, J_{45} = 16 Hz, H_5), 2.35–2.7 (m, 5, C_6H_5).

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.50; H, 6.25.

A sample of **42** was isomerized to **43** by treatment with iodine in benzene.

Irradiation of (*E,E*)-4-Methyl-6-phenyl-3,5-hexadienone (34).—Dienone **34** was prepared by treatment of the corresponding dienoic acid (**43**) with methyllithium (*vide supra*) and isolated as yellow crystals, mp 57–58° (lit.[47] 53°); phenylsemicarbazone derivative, mp 190–191° (cor) (lit.[47] 190°).

(43) K. v. Auwers and J. Henya, *Justus Liebigs Ann. Chem.*, **434**, 157 (1923).

(44) H. Rupe and W. Lotz, *Chem. Ber.*, **36**, 15 (1903).

(45) F. Dautwitz, *Monatsh. Chem.*, **27**, 775 (1906).

(46) J. L. Plati, W. H. Strain, and S. L. Warren, *J. Amer. Chem. Soc.*, **65**, 1273 (1943).

(47) C. H. Eugster, C. Garbers, and P. Karrer, *Helv. Chim. Acta*, **35**, 1179 (1952).

An ether solution 5.16×10^{-3} *M* in **34** was irradiated in a uv cuvette. Analysis by glpc (AC-1, 180°) showed **35** (T_r 14.2 min), **36** (T_r 25.2 min), and **34** (T_r 26.8 min). In addition there was an unidentified component at T_r 20.8 min, which comprised less than 1% of the total mixture and did not change in percentage composition over the course of the irradiation. In a preparative run, 0.476 g of **34** in 500 ml of ether (5.45×10^{-3} *M*) was irradiated for 45 min with RPR 3500A lamps. Removal of solvent left a yellow oil. Isomer **35** was collected by preparative glpc (PC-2, 180°) as a yellow oil.

Irradiation of (*Z*,*E*)-4-Methyl-6-phenyl-3,5-hexadienone (36).—Dienone **36** was prepared by treating **42** with methyllithium (*vide supra*) to give a yellow oil. An ether solution 1.7×10^{-3} *M* in **36** was irradiated in a uv cuvette. Glpc analysis (AC-1, 180°) revealed **34**, **35**, and **36** identical in retention times and photostationary-state concentrations with the three components obtained from irradiation of **34**.

Irradiation of *trans*-3-Styryl-2-cyclohexenone (37).—Compound **37** was prepared according to the general method of Crison and Normant.[41] A solution of 0.0805 g of **37** in 500 ml of ether (8.13×10^{-4} *M*) was irradiated with RPR 3500A lamps. After 10 min, the uv absorption maximum had decreased in intensity by a factor of 2 and shifted 15 nm to shorter wavelengths. Removal of solvent left pasty yellow solid. In another run, a solution of 0.2103 g of **41** in 500 ml of ether (2.12×10^{-3} *M*) was irradiated. Analysis by glpc (AC-1, 200°) of the photomixture showed **38** (T_r 19.6 min) and **37** (T_r 36.4 min). A steady state was reached after 10 min. Removal of solvent again gave a yellow paste from which **38** was isolated by preparative glpc (PC-2, 200°). Compound **38** was a yellow oil. Analysis by glpc showed the isomeric purity to be 92%.

Irradiation of *all-trans*-1-Phenyl-2,4-hexadienone (44).—To a 100-ml, round-bottom flask equipped with a reflux condenser were added 4.8 g (12.6 mmol) of benzoylmethylenetriphenylphosphorane,[48] 5 g of crotonaldehyde, and 50 ml of benzene. The solution was heated at reflux for 24 hr. Removal of solvent left a tan solid that was washed with two 20-ml portions of ether. The remaining solid (triphenylphosphine oxide) was discarded. Evaporation of the ether and sublimation (60°, 0.05 mm) gave 1.541 g (71%) of crude **44**, a yellow solid. Recrystallization from 20 ml of hexane gave light yellow crystals, mp 47–48.5° (lit.[49] 47–48°).

A solution of 0.0436 g of **44** in approximately 500 ml of ether (*ca.* 5×10^{-4} *M*) was irradiated with RPR 3500A lamps. A tenfold dilution with cyclohexane was made for uv samples.

Time, min	λ_{max}	Absorbance at λ_{max}
0	288	1.20
10	291	1.14
15	291	1.15
20	291	1.14

The samples were analyzed by glpc (AC-1, 175°). At zero time there appeared one trace at T_r 27.6 min (**44**). As the irradiation progressed, there appeared a trace assigned to **45** at T_r 26.4 min.

Irradiation of *trans*-1-Phenyl-5-methyl-2,4-hexadienone (46).—A solution of 4.8 g (12.6 mmol) of benzoylmethylenetriphenylphosphorane, 5 g of 3-methyl-2-butenal,[50] and 75 ml of dry benzene was heated at reflux for 24 hr in a nitrogen atmosphere. Removal of solvent left an amber mass which was washed with two 50-ml portions of ether. The remaining solid (triphenylphosphine oxide) was discarded. Evaporation of the washings left an amber oil which was filtered through 30 g of alumina with 100 ml of benzene–hexane (1:1). Removal of solvent and distillation gave 0.8 g (34%) of **46**, bp 113° (1 mm), as yellow crystals. Recrystallization from two 10-ml portions of hexane gave **46** as yellow crystals, mp 44.5–45°.

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.80; H, 7.50.

A solution of 0.0328 g of **46** in 500 ml of ether (3.54×10^{-4} *M*) was irradiated with RPR 3500A lamps. Analysis by glpc (AC-1, 175°) at zero time showed **39** (T_r 45.6 min) and a barely detectable trace at 20.4 min. After 20 min of irradiation time the trace at T_r 20.4 min was somewhat more defined than at zero time, but it contributed less than 3% to the total area under the two peaks. The uv spectrum of the solution did not change during irradiation.

Irradiation of *all-trans*-1-(*p*-Bromophenyl)-2,4-hexadienone (47).—A solution of 10 g (21.7 mmol) of *p*-bromobenzoylmethylenetriphenylphosphorane,[51] 5 g of crotonaldehyde, and 100 ml of dry benzene was heated at reflux for 24 hr. Removal of solvent left a tan solid which was washed with two warm 50-ml portions of benzene–hexane (1:1). The remaining solid was filtered through 50 g of alumina with 150 ml of benzene–hexane (1:1). Removal of solvent and recrystallization from two 50-ml portions of hexane gave **47** as 2.241 g (32.4%) of off-white plates, mp 109–110°.

Anal. Calcd for $C_{12}H_{11}OBr$: C, 57.39; H, 4.41; Br, 31.82. Found: C, 57.65; H, 4.70; Br, 31.60.

A solution of 0.151 g of **47** in 600 ml of deaerated ether (1×10^{-3} *M*) was irradiated with RPR 3500A lamps. An inert atmosphere was maintained throughout the irradiation. Analysis by glpc (AC-1, 200°) showed that at zero time there was **47** (T_r 20.8 min) and an impurity at T_r 15.6 min (*ca.* 3%). As the reaction proceeded, a new component assigned structure **48** appeared at T_r 20 min. An apparent photostationary state containing 10–20% **48** was set up between **47** and **48** after 10 min. The uv spectrum of this mixture in cyclohexane exhibited λ_{max} at 298 nm with 92% of the original intensity and shoulder at 292 nm (**47** exhibits two maxima of equal intensity at 298 and 292 nm). Within limits of error the area for the 15.6-min trace did not change during the irradiation. There was a slow decrease in total trace area for **47** and **48** over the course of the irradiation (equal injection volumes) such that after 30 min the total area was approximately 65% of the original area for **47**. Analysis of the reaction mixture by tlc (CCl_4) showed two spots at approximately R_f 0.5 (**47** and **48**), a small spot at R_f 0.8, and two small spots near the application point. Removal of solvent left a brown solid. The color and the low R_f components and the loss of volatile material (glpc) are indicative of decomposition and/or polymerization.

Registry No.—**6**, 18402-90-9; **8**, 16647-04-4; **13**, 29179-01-9; **19**, 29179-03-1; **21**, 29178-97-0; **24**, 29179-02-0; **27**, 29178-99-2; **29**, 29168-56-7; **29** semicarbazone, 29168-57-8; **30**, 29168-58-9; **31**, 29179-13-3; **33**, 29179-15-5; **36**, 29179-18-8; **37**, 29179-20-2; **42**, 20430-09-5; **44**, 29179-22-4; **46**, 29179-23-5; **47**, 29179-24-6; pseudoionone, 141-10-6.

(48) F. Ramiriez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).
(49) R. Kuhn and H. A. Staab, *Chem. Ber.*, **87**, 262 (1954).
(50) W. G. Young and S. L. Linden, *J. Amer. Chem. Soc.*, **69**, 2912 (1947).
(51) H. Strzelecka, M. S. Siemiatycki, and C. Prevost, *C. R. Acad. Sci.*, **254**, 696 (1962).

Notes

Synthesis and Fragmentation Reactions of 7,7-Dimethoxy-1,2,3,4-Tetrachlorobenznorbornadiene. A Convenient Route to 7-Benznorbornenone

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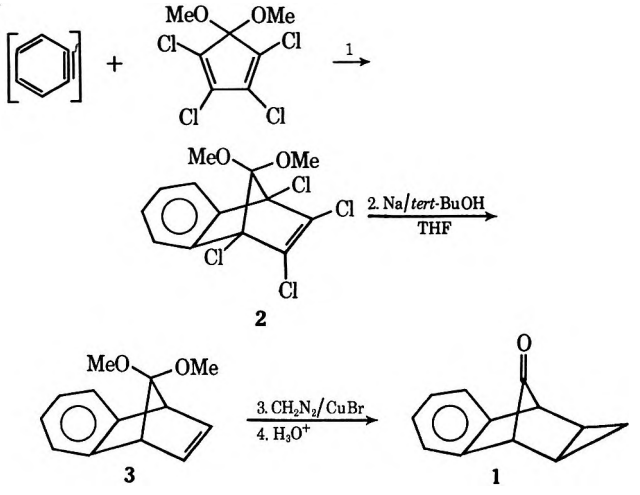
Received October 13, 1970

Current investigations in our laboratory of the homoconjugative reinforcing effects of favorably disposed cyclopropyl groups have required the facile synthesis of benznorbornadiene derivatives bearing oxygenated substituents at the bridge carbon. Previous work[2] utilizing the Cu(I)-catalyzed reaction of benzoyl peroxide or *tert*-butyl perbenzoate with benznorbornadiene afforded such derivatives, albeit not without difficulties. The reaction sequence illustrated in Scheme I appeared

SCHEME I



to offer an attractive alternative approach to the tricyclo[3.2.1.$0^{2,4}$]octenone **1**,[3] and this report describes the initial results of an attempted application of this synthetic scheme (steps 1 and 2) as well as some interesting thermal and electron impact induced fragmentations of 7,7-dimethoxy-1,2,3,4-tetrachlorobenznorbornadiene (**2**).

The adduction of benzyne with 5,5-dimethoxy-1,2,3,-4-tetrachlorocyclopentadiene[4] afforded adduct **2** in 49% yield.[5] Mass spectral examination (70 eV) of **2** failed to reveal a molecular ion (*m/e* 338); however, an intense peak (base peak) was observed at *m/e* 303 corresponding to the loss of chloride. The isotopic peak ratios (*m/e* 305, 307, and 309) were in accord with that predicted for a fragment ion containing three chlorine atoms. The remaining fragment ions of major interest and their relative abundance are recorded in Table I.

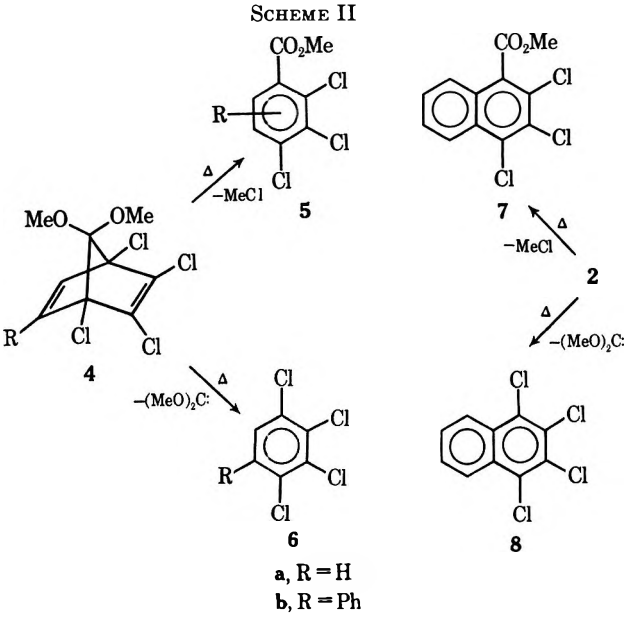
TABLE I

RELATIVE ABUNDANCES OF THE MAJOR IONS IN THE MASS SPECTRA (70 eV) OF **2** AND **4a**

	2		**4a**	
Ion	*m/e*	Relative abundance	*m/e*	Relative abundance
$M^+ - Cl$	303	100	253	100
$M^+ - CH_3Cl$	288	15	238	3
$M^+ - C_2H_6O_2$	264	20	214	8
$M^+ - C_2H_6O_2Cl$	257	43	207	100
$M^+ - C_3H_6O_2Cl$	229	17	179	28
$C_2H_3O_2$	59	30	59	100

The facile loss of chloride from **2** on electron impact appears related mechanistically to thermal fragmentation of the chlorinated norbornadienone ketals **4a**[6] and **4b**[7,8] to the corresponding trichlorobenzoates **5a** and **5b** and methyl chloride (Scheme II). Furthermore, on

SCHEME II



electron impact ketal **4a** displays an identical assortment of fragment ions (Table I) with the highest mass ion (*m/e* 253, base peak) again formed by loss of chloride. On this basis we formulate the M − 35 ion from **2** as the trichloroaryldimethoxycarbinyl cation **a** as shown in Scheme III.[9] Subsequent loss of dimethyl

(1) (a) National Science Foundation Cooperative Predoctoral Fellow, 1966–1970; (b) Alfred P. Sloan Foundation Fellow.

(2) M. E. Brennan and M. A. Battiste, *J. Org. Chem.*, **33**, 324 (1968).

(3) M. A. Battiste and M. E. Brennan, *Tetrahedron Lett.*, 5857 (1966).

(4) J. S. Newcomer and E. T. McBee, *J. Amer. Chem. Soc.*, **71**, 946 (1949).

(5) See J. W. Wilt and E. Vasiliauskas, *J. Org. Chem.*, **35**, 2410 (1970), for a similar preparation of **2** reported while our study was in progress.

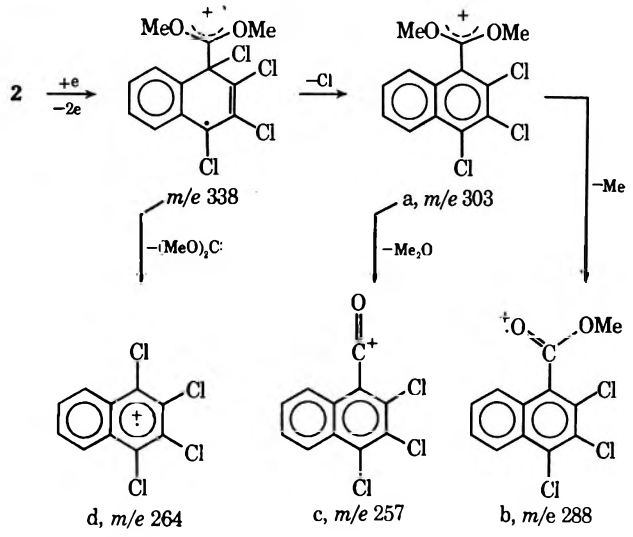
(6) K. McKenzie, *J. Chem. Soc.*, 5710 (1964).

(7) R. W. Hoffman and H. Hauser, *Tetrahedron Lett.*, 197 (1964).

(8) (a) D. M. Lemal, E. P. Gosselink, and A. Ault, *ibid.*, 579, (1964); (b) D. M. Lemal, E. P. Gosselink, and S. D. McGregor, *J. Amer. Chem. Soc.*, **88**, 582 (1966).

(9) Since the molecular ion of **2** was unobserved it is perhaps unreasonable to discuss the structure of this ion, as loss of chloride or dimethoxycarbene may be nearly simultaneous with electron impact. It is therefore purely for the sake of convenience that we represent the structure of this ion in Scheme III as that of the bridge-opened cation radical.

SCHEME III



ether or methyl from this ion leads to ions b (*m/e* 288) and c (*m/e* 257) respectively. Similar structures may be accorded to fragment ions *m/e* 253, *m/e* 238, and *m/e* 207 analogously derived from **4a**.

Complete scission of the dimethoxymethano bridge on electron impact is seen to be a relatively less important process than chloride loss at least for the annelated ketal **2**. Though the $M^+ - C_3H_6O_2$ ion from **4a** is even less intense than that from **2** the larger intensity for the *m/e* 59 ion, presumably derived from the bridge fragment, complicates the picture for **4a**, while suggesting that bridge scission and chloride loss from the molecular ion (*m/e* 288) are competitive. The latter conclusion compares favorably with the reported[6] product distribution (Table II) from thermal decomposition (85°)

TABLE II

AROMATIZATION OF SOME 7-NORBORNADIENONE KETALS. PRODUCT DISTRIBUTION

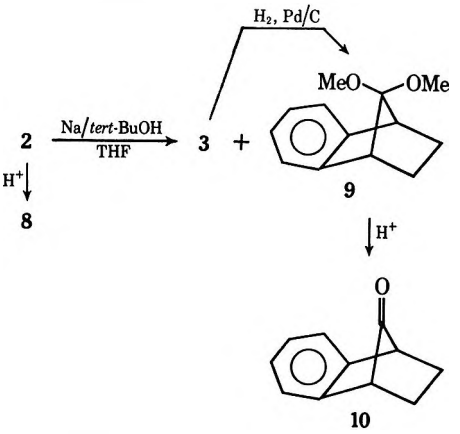
Ketal	Solvent	T, °C	Rel wt % —aromatic products— Ester[a]	Chloroaromatic[b]
4a[c]	Neat	85	56.7	43.3
4b[d]	Cyclohexane	145	7.1	92.9
4b[d]	Acetonitrile	115	87.5	12.5
2[e]	Decalin	193	6.5	93.6
2[e]	Acetonitrile	145–155[f]	85	15

[a] Refers to the corresponding ester **5a**, **5b**, or **7**. [b] Refers to the corresponding chloroaromatic **6a**, **6b**, or **8**. [c] Reference 6. [d] Reference 8b. [e] This work. [f] See Experimental Section.

of neat **4a**. By varying the solvent polarity, however, either process, extrusion of dimethoxycarbene or loss of methyl chloride, may become the predominant reaction course[10] as clearly revealed by the two entries for **4b** in Table II.

For comparison, the thermal fragmentation of **2** was examined in two solvents, decalin and acetonitrile, of widely differing polarity. While the distribution of the expected products **7** and **8** in the two solvents was very similar to that found for **4b**, the enhanced stability of **2** as revealed by the higher decomposition temperatures was surprising. Thus **2** was essentially unchanged after 14 hr at 100° in hexachlorobutadiene, conditions which far exceed that required for decomposition of **4a** (see Experimental Section). Furthermore, a crude rate determination in acetonitrile at 115° revealed that bridge cleavage in **2** was slower than that found for **4b**[8b] by a factor of *ca.* $10^{2.6}$. Although more precise kinetic data may be desirable, the magnitude of the observed annelation effect is sufficient to warrant reopening of the question of simultaneity of the requisite bond fragmentations.[11]

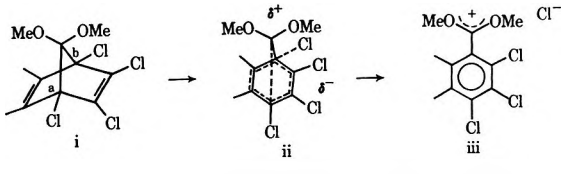
Dechlorination of **2** using sodium in *tert*-BuOH/THF[12] resulted in partial reduction of the olefinic moiety to yield a nearly 1:1 mixture of **3** and the corresponding saturated ketal **9**. Attempted separation



of the two ketals by a variety of techniques proved unyielding. Monitoring of the dechlorinated products by glpc during the course of reaction indicated that **3** and **9** are formed simultaneously, thus ruling out further reduction of **3** under the reaction conditions. Identification of **9** in the reaction mixture was achieved by nmr analysis and subsequent catalytic hydrogenation of the dechlorinated mixture to pure **9**. Acid hydrolysis of **9** yielded the known[13] 7-benznorbornenone (**10**) in good yield. The overall yield of **10** by this process (*ca.* 27%) compares favorably with that reported[14] for a recently improved synthetic route to **10**. Thus, although an improved route to cyclopropyl ketone **1** was not realized, a convenient alternate synthesis of **10** has been developed inadvertently.

(10) See ref 8b for an excellent discussion of the mechanistic alternatives suggested by these solvent effects. Homopolar or heteropolar one-bond cleavages, depending on solvent, are postulated for the rate-determining step.

(11) Lemal and coworkers had earlier[8b] ruled out the possibility of concerted fragmentation of **4b** to **6b** in nonpolar solvents on the basis of poor overlap of the bridge orbitals with the 1,4-diene system. However, while this may be partially true for the ground state, the geometry of the transition state may be sufficiently altered so as to allow six-center orbital overlap that begins to approach that for the fully aromatized ring. Furthermore, without too severely stretching the theme of the latter argument, one can visualize an unsymmetrical transition state for formation of ion pair iii that likewise has a high degree of concertedness. Thus, if the breaking of bond a in i results in a flattening of the ring, a concomittant loosening of bond b may occur leading smoothly to transition state ii in which the breaking of bond a



is considerably advanced over that for bond b. Transition state ii permits some cyclic delocalization while at the same time allowing for appreciable charge dispersal which may help to explain the rather small rate enhancements observed for this process in going from a nonpolar to polar solvent.

(12) P. G. Gassman and J. L. Marshall, *Org. Syn.*, **48**, 68 (1968).

(13) P. D. Bartlett and W. P. Giddings, *J. Amer. Chem. Soc.*, **82**, 1240 (1960).

(14) R. Muneyuki and H. Tanida, *J. Org. Chem.*, **31**, 1988 (1968).

Experimental Section[15]

7,7-Dimethoxy-1,2,3,4-tetrachlorobenznorbornadiene (2).—A mixture of 24.3 g (0.092 mol) of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene,[4] 5.67 g (0.031 mol) of 2-carboxybenzenediazonium chloride, 250 ml of 1,2-dichloroethane, and 7 ml of propylene oxide was stirred at reflux for 2 hr. The solvent was removed on a rotary evaporator and the residue was chilled until crystalline. Recrystallization from isooctane gave 2.1 g of **2**, mp 121–123°; a second crop, 0.3 g, mp 110–114° was obtained. Distillation of the mother liquor at 85–92° (2–3 mm) afforded 6.93 g of starting material. Chromatography of the residue on standard alumina using 20% benzene–hexane followed by treatment as before gave 2.7 g of product (5.1 g overall, 49% based on diazonium salt) and 7.64 g of starting material. Three recrystallizations from isooctane gave analytically pure **2** as white crystals: mp 123–124°; nmr (CCl_4) τ 6.82 (3, s), 6.42 (3, s), 2.5–2.9 (4, m).

Anal. Calcd for $C_{13}H_{10}O_2Cl_4$: C, 45.89; H, 2.96; Cl, 41.73. Found: C, 46.12; H, 3.02; Cl, 41.75.

Thermal Fragmentation of 7,7-Dimethoxy-1,2,3,4-tetrachlorobenznorbornadiene (2). A. Nonpolar Solvent.—A quantity of **2** was dissolved in hexachlorobutadiene, placed in an nmr tube, and immersed in a constant-temperature bath. Periodic analysis revealed no change in the spectrum up to 14 hr at 100°. After 20 hr at 150–160°, *ca.* 25% of the starting ketal still remained. Immersion of the tube in boiling decalin (bp 193°) for 2 hr resulted in the formation of crystalline material which negated further nmr examination. On the preparative scale 0.300 g (0.882 mmol) of **2** and 4 ml of freshly distilled decalin (bp 193°) were refluxed for 2 hr. At the end of this time, the reaction was cooled to room temperature and 0.123 g of white needles, mp 195–197°, was collected by filtration and washed with hexane. Chromatography of the combined filtrate on silica gel using hexane afforded decalin and another component. Elution with benzene gave 0.030 g of a heavy yellow oil, the major portion of which (55%) consisted of methyl 2,3,4-trichloro-1-naphthoate (**7**): nmr (CCl_4) τ 6.00 (3, s), 2.40 (3, m), 1.75 (1, m); $\nu_{C=O}$ 1725 cm^{-1}. Elution with ether gave 0.023 g of a heavy yellow oil whose nmr suggested it contained products originating from the extruded dimethoxymethano bridge. Rechromatography of the hexane fraction on alumina to remove decalin gave on elution with benzene 0.097 g of white solid, identical with the initially isolated white needles and with authentic 1,2,3,4-tetrachloronaphthalene (**8**) prepared by the acid hydrolysis of **2**. The overall yield of **8** from thermolysis of **2** was 0.220 g (93.6%): nmr ($CDCl_3$) τ 2.4 (2, m) and 1.8 (2, m).

B. Polar Solvent.—A mixture of 75 mg of **2** (0.22 mmol) and 1 ml of acetonitrile was sealed in a nmr tube and immersed in a constant-temperature bath at 115°. Periodic analysis of the nmr spectrum revealed the formation of a new singlet at τ 6.00. Determination of the relative integral ratios of the original methyl absorptions of **2** and that of the new singlet with time provided an approximate rearrangement rate of 3×10^{-6} sec^{-1}. After 44 hr (0.7 half-lives), the contents of the nmr tube were sealed in a thick-walled Carius tube and heated in an oil bath at 145–155° for 14 hr. Removal of solvent gave 52 mg of yellow-white crystals whose nmr spectrum indicated that the material was predominantly methyl ester **7**. Chromatography on silica gel with hexane afforded 8 mg of white solid whose ir spectrum was identical with that of authentic **8**. Further elution with benzene afforded 41 mg of yellow-white crystals, mp 90–92°. Recrystallization from *n*-hexane gave mp 96.5–97.5°. Analysis of the nmr and ir spectra confirmed that the product was methyl 2,3,4-trichloro-1-naphthoate (**7**).

Anal. Calcd for $C_{12}H_7O_2Cl_3$: C, 49.78; H, 2.42. Found: C, 49.99; H, 2.51.

Thermal Fragmentation of 7,7-Dimethoxy-1,2,3,4-tetrachloronorbornadiene (4a).—A quantity of **4a**[6] was dissolved in hexachlorobutadiene, placed in an nmr tube, and immersed in a constant-temperature bath at 100°. Analysis of the spectrum after 3 hr revealed complete disappearance of the vinylic protons for **4a**.

Dechlorination of 2.—To a vigorously stirred mixture of 6.0 g (0.018 mol) of **2**, 14.7 g of *tert*-butyl alcohol (distilled from sodium) and 105 ml of tetrahydrofuran (distilled from lithium aluminum hydride), there was added, in an argon atmosphere, 10.9 g (0.471 g-atom) of freshly cut sodium metal. The mixture was stirred at reflux for 8.5 hr and methanol then added cautiously to destroy excess sodium. The reaction was poured onto 200 g of ice and the reaction flask was washed with 200 ml of water. The mixture was extracted with three 100-ml portions of ether and the combined extracts were washed with three portions of water and one portion of saturated NaCl solution. The ethereal solution was dried over $MgSO_4$ and filtered. Removal of solvent on a rotary evaporator gave a yellow oil which, upon chilling, gave 0.4 g of white crystals, mp 43–45°, after thorough washing with hexane. Distillation of the mother liquor at 83–86° (1.5–2.0 mm) gave 2.6 g (3.0 g overall, 84%) of a colorless oil whose nmr spectrum was identical with that of the white crystals. Glpc analysis at 150° (5 ft × 1/8 in. 5% SE-30 column) indicated the presence of two components in *ca.* equal proportions, data consistent with nmr integral ratios. Attempted separations by column chromatography and $AgNO_3$ partition extraction were only partially successful. The nmr (CCl_4) spectrum of 7,7-dimethoxybenznorbornadiene showed the methoxy protons as singlets at τ 7.08 and 6.88, two bridgehead protons as a triplet at 6.17, two olefinic protons as a triplet at 3.45, and four aromatic protons as an A_2B_2 multiplet at 3.01.

7,7-Dimethoxybenznorbornene (9).—A 3.28-g sample of the dechlorinated ketal mixture (estimated to contain 1.64 g, 8.1 mmol, of unsaturated ketal) in 30 ml of methanol was hydrogenated at room temperature with 150 mg of 10% Pd/C as catalyst. Hydrogenation was complete in about 35 min with an uptake of about 225 ml (*ca.* 10 mmol) of hydrogen. The solution was filtered through a pad of Celite, and, on removal of solvent, a brownish oil was obtained. Chromatography on standard alumina with hexane gave 2.5 g (76%) of a colorless oil which solidified upon standing, mp 45–48°. Two recrystallizations from petroleum ether (bp 20–40°) gave 7,7-dimethoxybenznorbornene (**9**): mp 54–54.8°; nmr ($CDCl_3$) τ 8.86 (2, m), 7.90 (2, m), 6.91 (3, s), 6.81 (5, broad singlet), 2.96 (4, s).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.54; H, 7.98.

7-Benznorbornenone (10).—A mixture of 150 mg (0.735 mmol) of ketal **9**, 4 ml of tetrahydrofuran, and 2 ml of concentrated H_2SO_4 was stirred at room temperature for 2 hr. At the end of this time, the dark red solution was poured into water and the aqueous mixture was extracted three times with ether. The combined extracts were dried and filtered, and the solvent was removed on a rotary evaporator to give a dark yellow oil which was percolated through a column of standard alumina with ether. Removal of solvent gave 0.101 g (87%) of 7-benznorbornenone (**10**) [nmr (CCl_4) τ 2.83 (4, s), 6.75 (2, t), 7.87 (2, m), 8.68 (2, m)], identical with an authentic sample prepared by chromium trioxide oxidation of *anti*-7-benznorbornenol, mp 101–103° (lit.[13] mp 103–104°), obtained from catalytic hydrogenation of *anti*-7-benznorbornadienol.[3] The 2,4-dinitrophenylhydrazone of **10** gave yellow crystals from ethanol, mp 152–152.5° (lit.[13] mp 143.6–146.4°).

Registry No.—**2**, 24472-15-9; **7**, 29261-09-4; **9**, 29370-70-5; **10**, 6165-88-4.

Acknowledgment.—Support of this work by the National Science Foundation (GP-9412) is gratefully acknowledged.

(15) Melting points were determined with a Thomas-Hoover apparatus. All melting and boiling points were uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Atlantic Microlab, Inc., Atlanta, Ga. Vapor phase chromatographic analyses were performed with an Aerograph Model 600-D instrument equipped with a hydrogen flame ionization detector. Infrared spectra were recorded on either a Perkin-Elmer 137 or Beckman IR-10 instrument. Solid samples were examined as Nujol mulls while liquid samples were examined neat on sodium chloride plates. Nmr spectra were obtained on a Varian A-60A instrument using tetramethylsilane as an internal reference. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E instrument.

Synthesis of Dithienothiophenes

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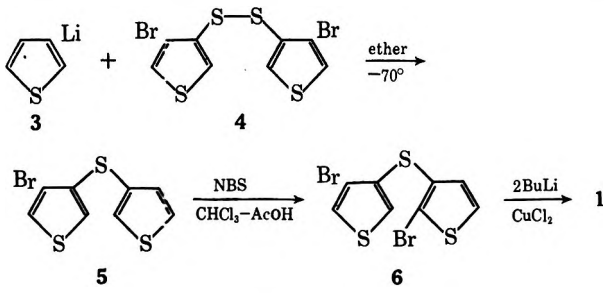
Recently we reported the synthesis of four of the six possible dithienothiophene isomers.[1] The two remain-

(1) F. de Jong and M. J. Janssen, *J. Org. Chem.*, **36**, 1645 (1971).

ing compounds **1** and **2** could not be prepared by the same procedure because of the instability of 2-bromo-3-thienyllithium.[2] Selective bromination reactions have been used now to prepare dithieno[3,2-*b*:3′,4′-*d*]thiophene (**1**) and dithieno[2,3-*b*:2′,3′-d]thiophene (**2**).

1 **2**

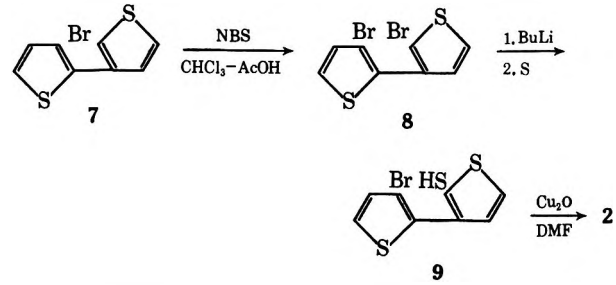
From the reaction of 3-thienyllithium[3] (**3**) with 4,4′-dibromo-3,3′-dithienyl disulfide[1] (**4**) in ether at −70°, 4-bromo-3,3′-dithienyl sulfide (**5**) was isolated. Treatment of sulfide **5** with *N*-bromosuccinimide (NBS) in a chloroform–acetic acid mixture[4] afforded 2,4′-dibromo-3,3′-dithienyl sulfide (**6**). The nmr spectrum confirmed that bromination had occurred in the 2 position, since two pairs of doublets were observed with



3 **4** **5** **6**

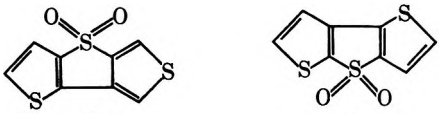
J = 3.4 Hz (2,5 coupling) and J = 5.6 Hz (2,3 coupling). Dilithiation of **6** followed by oxidative ring closure gave the dithienothiophene **1** in 13% overall yield. The compound was characterized by elementary analysis and the nmr spectrum showed the correct coupling constants ($J_{2,3}$ = 5.1 and $J_{2,5}$ = 2.5 Hz).

Dithieno[2,3-*b*:2′,3′-*d*]thiophene (**2**) was prepared starting from 3-bromo-2,3′-dithienyl (**7**).[5] On treatment with *N*-bromosuccinimide **7** was almost quantitatively converted to 2,3′-dibromo-3,2′-dithienyl (**8**), which on monolithiation followed by reaction with sulfur yielded the intermediate thiol, presumably **9**. Because of thermal instability, the thiol was not isolated but directly treated with cuprous oxide in dimethylformamide[6] to give dithienothiophene **2** in 65% overall yield. The structure of **2** was supported by elementary analysis and its nmr spectrum, showing two AB systems with J = 5.0 Hz (2,3 coupling).



7 **8** **9**

In the case of the other four dithienothiophenes, the sulfur atom of the central ring has been proved[1] to be the most reactive toward oxidizing agents. In accordance with these results, compounds **1** and **3** were oxidized by *m*-chloroperbenzoic acid to the corresponding sulfones **10** and **11**, as was indicated by the ir spectra



10 **11**

(SO_2 absorptions at 1130 and 1300 cm^{-1}) and the nmr spectra ($J_{2,3}$ and $J_{2,5}$ do not change significantly upon oxidation).

Experimental Section

All experiments with lithio compounds were conducted in a dry N_2 atmosphere. Melting points are uncorrected. Nmr spectra were recorded on a Varian A-60 instrument with TMS as internal standard. Uv spectra were determined with a Zeiss PMQ II and infrared spectra were run on a Unicam SP 200. The microanalyses were carried out in the analytical section of this department under direction of Mr. W. M. Hazenberg.

4-Bromo-3,3′-dithienyl Sulfide (5).—A solution of 3-thienyllithium was prepared at −70° from 21.3 g (0.13 mol) of 3-bromothiophene[7] in 250 ml of absolute ether and 100 ml of 1.3 *N* ethereal *n*-BuLi (0.13 mol). The mixture was transferred to an externally cooled dropping funnel and added during 30 min to a stirred suspension of 50.0 g (0.13 mol) of the disulfide **4** cooled to −70°. After stirring at −70° for 2.5 hr, the mixture was allowed to warm and 200 ml of water was added. The ether layer was separated, washed with water, dried ($MgSO_4$), and concentrated. Distillation of the residue yielded 29.0 g (80%) of **5**: bp 132–134° (0.04 mm); $n^{20}D$ 1.6930; nmr (CD_3COCD_3) δ 7.0–7.5 (m); uv max (EtOH) 265 mμ (log ε 3.67).

Anal. Calcd for $C_8H_5S_3Br$: C, 34.66; H, 1.82; S, 34.70; Br, 28.83. Found: C, 34.96; H, 2.00; S, 34.50; Br, 29.19.

2,4′-Dibromo-3,3′-dithienyl Sulfide (6).—To a stirred solution of 15.0 g (0.054 mol) of **5** in 500 ml of a mixture of chloroform–acetic acid (1:1) was added in small portions 9.8 g (0.055 mol) of *N*-bromosuccinimide. The mixture was stirred at room temperature for 3 hr, then water was added, and the chloroform layer separated, washed with aqueous KOH solution, again with water, and dried ($MgSO_4$). Evaporation of the solvent left a solid residue which was recrystallized from ether–pentane (1:1) yielding 16 g (84%) of **6**: mp 33–34°; nmr (CD_3COCD_3) δ 7.63 (d, 1, J = 5.8 Hz), 7.37 (d, 1, J = 5.8 Hz), 7.50 (d, 1, J = 3.4 Hz), 6.78 (d, 1, J = 3.4 Hz); uv max (EtOH) 234 mμ (log ε 3.96), 278 (3.72).

Anal. Calcd for $C_8H_4S_3Br_2$: C, 26.98; H, 1.13; S, 27.01; Br, 44.88. Found: C, 27.02; H, 1.27; S, 26.74; Br, 45.03.

Dithieno[3,2-*b*:3′,4′-*d*]thiophene (1).—To a solution of 16.0 g (0.045 mol) of sulfide **6** in 150 ml of absolute ether cooled to −70° was added 70 ml of a 1.3 *N* ethereal *n*-BuLi solution (0.091 mol). After stirring at −70° for 30 min, the mixture was transferred to an externally cooled (−70°) dropping funnel and added in a slow stream to a vigorously stirred suspension of 17 g (0.10 mol) of anhydrous $CuCl_2$ in 250 ml of absolute ether cooled to −30°. The mixture was stirred overnight, water was added, and the Cu_2Cl_2 precipitation was filtered. The ether layer was separated, washed with 2 *N* HCl and then water, and dried ($MgSO_4$). After evaporation of the ether, the residual oil was purified through the picrate yielding 1.7 g (19%) of **1** as colorless needles from methanol: mp 55–55.5°; nmr (CD_3COCD_3) δ 7.63 (d, 1, J = 2.5 Hz), 7.52 (d, 1, J = 2.5 Hz), 7.58 (d, 1, J = 5.1 Hz), 7.22 (d, 1, J = 5.1 Hz); uv max (EtOH) 223 mμ (log ε 3.95), 250 (4.02), 265 (3.96), 285 (4.11), 296 (4.16), 315 (3.69).

Anal. Calcd for $C_8H_4S_3$: C, 48.95; H, 2.06; S, 49.00. Found: C, 49.13; H, 2.08; S, 48.98.

2,3′-Dibromo-3,2′-dithienyl (8).—From 4.40 g (0.018 mol) of 3-bromo-2,3′-dithienyl[5] and 3.2 g (0.018 mol) of *N*-bromosuccinimide, the procedure described for the synthesis of 6 yielded 4.8 g (83%) of **8**: mp 54–55° (from methanol); nmr ($CDCl_3$) δ 7.28 (d, 1, J = 5.2 Hz), 7.08 (d, 1, J = 5.2 Hz), 7.33 (d, 1, J = 5.5 Hz), 7.03 (d, 1, J = 5.5 Hz); uv max (EtOH) 242 mμ (log ε 4.10), 285 (3.59).

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Anal. Calcd for $C_8H_4Br_2S_2$: C, 29.65; H, 1.24; S, 19.79; Br, 49.32. Found: C, 29.89; H, 1.40; S, 19.78; Br, 49.40.

2-Mercapto-3′-bromo-2′,3-dithienyl (9).—To a solution of 3.89 g (0.012 mol) of dithienyl **8** in 125 ml of absolute ether cooled to −70° was added 7.5 ml of a 1.6 *N* ethereal *n*-BuLi solution (0.012 mol). The mixture was stirred for 45 min and then 0.42 g (0.013 mol) of dry sulfur was added and stirred for another 45 min at −30°. After addition of water, the ether layer was extracted with 100 ml of 2 *N* NaOH solution. The combined aqueous layers were acidified and extracted with ether; the ether layer was washed with water and dried ($MgSO_4$). Evaporation of the ether left 2.9 g (88%) of a yellow oil. Further attempts of purification led to decomposition: nmr (CD_3COCD_3) δ 7.65 (d, 1, J = 5.3 Hz), 7.11 (d, 1, J = 5.3 Hz), 7.17 (d, 1, J = 5.3 Hz), 7.57 (d, 1, J = 5.3 Hz), 3.08 (s, 1, SH); ir (liquid) 2550 cm^{-1} (SH).

Dithieno[2,3-*b*:2′,3′-*d*]thiophene (2).—To a suspension of 0.54 g (9.5 mmol) of KOH and 0.62 g (4.8 mmol) of Cu_2O in 300 ml of dry dimethylformamide (DMF) was added during 1 hr a solution of 2.60 g (9.4 mmol) of freshly prepared thiol **8** in 20 ml of dry DMF. The mixture was heated under reflux for 45 hr. Most of the DMF was removed *in vacuo* and the residue dissolved in a benzene–pentane (1:1) mixture. The solution was washed with 4 *N* HCl solution and water and dried ($MgSO_4$). Evaporation left a white solid which on recrystallization from ether–hexane yielded 1.65 g (90%) of the dithienothiophene **2**: mp 53–54°; nmr (CD_3COCD_3) δ 7.42 (d, 1, J = 5.0 Hz), 7.60 (d, 1, J = 5.0 Hz), 7.36 (d, 1, J = 5.0 Hz), 7.52 (d, 1, J = 5.0 Hz); uv max (EtOH) 253 mμ (log ε 4.30), 266 (4.23), 278 (4.06).

Anal. Calcd for $C_8H_4S_3$: C, 48.95; H, 2.06; S, 49.00. Found: C, 48.91; H, 2.12; S, 48.70.

Dithieno[3,2-*b*:3′,4′-*d*]thiophene 4,4-Dioxide (10).—A solution of 175 mg (0.9 mmol) of dithienothiophene **1** and 350 mg (2.0 mmol) of *m*-chloroperbenzoic acid in 50 ml of dry dichloromethane was allowed to stand 14 hr at −15°. The solution was washed with 25 ml of a saturated $NaHCO_3$ solution and water and dried ($MgSO_4$). Evaporation of the solvent and recrystallization of the residue yielded 155 mg (75%) of **10** as colorless needles from ethanol: mp 234–235°; nmr (CD_3COCD_3) δ 7.75 (d, 1, J = 2.4 Hz), 8.16 (d, 1, J = 2.4 Hz), 7.35 (d, 1, J = 5.4 Hz), 7.72 (d, 1, J = 5.4 Hz); ir (KBr) 1130, 1290 cm^{-1} (SO_2); uv max (EtOH) 225 mμ (log ε 4.24), 250 (sh), 284 (3.97), 294 (4.00), 315 (3.65).

Anal. Calcd for $C_8H_4S_3O_2$: C, 42.08; H, 1.76; S, 42.13. Found: C, 42.14; H, 1.72; S, 42.28.

Dithieno[2,3-*b*:2′,3′-*d*]thiophene 4,4-Dioxide (11).—From 196 mg (1 mmol) of **2** and 400 mg (2.2 mmol) of *m*-chloroperbenzoic acid, the procedure described above yielded 150 mg (65%) of the sulfone **11**: mp 185–186°; nmr (CD_3COCD_3) δ 8.02 (d, 1, J = 5.0 Hz), 7.42 (d, 1, J = 5.0 Hz), 7.73 (d, 1, J = 5.2 Hz), 7.40 (d, 1, J = 5.2 Hz); ir (KBr) 1140, 1280 cm^{-1} (SO_2); uv max (EtOH) 250 mμ (log ε 4.25), 342 (3.53).

Anal. Calcd for $C_8H_4S_3O_2$: C, 42.08; H, 1.76; S, 42.13. Found: C, 42.06; H, 1.86; S, 41.90.

Registry No.—**1**, 29127-68-2; **2**, 236-65-7; **5**, 29127-70-6; **6**, 29127-71-7; **8**, 29127-72-8; **9**, 29127-73-9; **10**, 29127-74-0; **11**, 29127-75-1.

Electrolytic Dechlorination of Perchlorinated Styrene and Vinylpyridines

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Our interest in the selective dehalogenation of perhalogenated aromatic compounds has prompted us to investigate the electrochemical reduction of a number of such compounds. Results with the reduction of perchlorinated styrene and vinylpyridines, which we report here, have led to a simple method for making chloroaromatic acetylene derivatives in good yield and, in addition, demonstrate the probable order of occurrence of multiple reduction steps in compounds substituted in both the ring and side chain with chlorine.

The electrolytic reduction of octachlorostyrene (**1**) at a moving mercury cathode, carried out in 1:1 methanol–dimethoxyethane containing 5% water and ammonium acetate electrolyte, resulted in the isolation of pentachloroethynylbenzene (**2**) in 21% yield. There was also isolated from the crude product small amounts of β,β,2,3,4,5,6-heptachlorostyrene (**3**) and 2,3,5,6-tetrachloroethynylbenzene (**4**). Table I lists the improved

TABLE I

PRODUCT DISTRIBUTION AND YIELD FROM THE ELECTROLYTIC REDUCTION OF OCTACHLOROSTYRENE (**1**)[a]

Run	Electrolyte	Crude product, mol % by glc $C_6Cl_5C{\equiv}CH$ (**2**)	$C_6Cl_5CH{=}CCl_2$ (**3**)	$C_6HCl_4C{\equiv}CH$ (**4**)	Isolated yield of **2**, %
1 (Hg)	NH_4OAc	34.6	22.8	9.9	21
2 (Pb)	NH_4OAc–NH_3	69.8	7.9	22.4	60
3 (Pb)	NH_4OAc–NH_3	54.3	5.0	40.7	45
4 (Pb)	NH_4Cl	80.2	17.5	2.2	77
5 (Pb)	HCl	69.2	23.6	7.1	...[b]

[a] Figures are corrected for unreacted octachlorostyrene (~20% in all cases). [b] Product was not isolated.

results and product distributions obtained under different conditions (but all run in 1:1 methanol–dimethoxyethane solvent). Use of a lead cathode clearly increased the yield of the ethynylbenzene **2** and the cleanness of the reaction. The data also indicate that the yield of the by-product **3** is minimized by using buffered basic conditions (runs 2 and 3) while the amount of overreduction leading to **4** is minimized by using nearly neutral or slightly acidic conditions (runs 4 and 5).

In a few cases (illustrated by run 3) a greater amount of the overreduced product **4** was obtained at the same conversion level. This lack of reproducibility was partially alleviated by use of a spongy lead cathode,[2] which offers a greater surface area for the same size cathode. When the reaction was deliberately carried to overreduction, the resulting product was a mixture of the tetrachloroethynylbenzene **4** and 2,3,5,6-tetrachlorostyrene (**5**).

The results indicate that the following steps occur

$$C_6Cl_5C{\equiv}CCl + Cl^-$$
$$\overset{a}{\nearrow}$$
$$C_6Cl_5CCl{=}CCl_2 + 2e^- \longrightarrow Cl^- + [C_6Cl_5\bar{C}{=}CCl_2] \quad (1)$$
$$\underset{b}{\searrow}\ H^+$$
$$C_6Cl_5CH{=}CCl_2$$

$$C_6Cl_5C{\equiv}CCl + 2e^- + H^+ \longrightarrow C_6Cl_5C{\equiv}CH + Cl^- \quad (2)$$

$$C_6Cl_5C{\equiv}CH + 2e^- + H^+ \longrightarrow C_6HCl_4C{\equiv}CH + Cl^- \quad (3)$$

$$C_6HCl_4C{\equiv}CH + 2e^- + 2H^+ \longrightarrow C_6HCl_4CH{=}CH_2 \quad (4)$$

(1) Department of Environmental Toxicology, University of California, Davis, Calif. 95616.

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TABLE II
SUMMARY OF COMPOUND PROPERTIES

Compd[a]	Mp, °C	Ir, cm^{-1}	Nmr, ppm	C, % Calcd	C, % Found	H, % Calcd	H, % Found	Cl, % Calcd	Cl, % Found
$C_6Cl_5CH=CCl_2$ (3)	108–109	1600 (C=C)	6.66	27.8	27.9	0.3	0.5	71.9	71.5
$C_6HCl_4C\equiv CH$ (4)[b]	67–74	3220 (≡CH), 2250 (C≡C)	3.76 (≡CH), 7.49 (PhH)					60.4	59.2
$C_6HCl_4CH=CH_2$ (5)	46–49	1540 (C=C)	5.5–6.9 m ($CH=CH_2$), 7.47 (PhH)	40.0	39.4	1.7	1.6	58.5	85.6
2-$Cl_4PyC\equiv CH$ (7a)	108–111	3220 (≡CH), 2220 (C≡C)	3.55	34.9	35.1	0.4	0.6	58.8	59.0
3-$Cl_4PyC\equiv CH$ (7b)	85–88	3300 (≡CH), 2120 (C≡C)	3.86	34.9	34.7	0.4	0.5	58.8	59.0
trans-2-$Cl_4PyCH=CHCl$ (8)	117–121	1600 (C=C)	7.31 q (J = 12 cps)	30.3	30.4	0.7	0.7	63.9	63.8
trans-$C_6Cl_5CCl=CHCl$ (9)	109–110	1595 (C=C)	6.67	27.8	27.4	0.3	0.3	71.9	71.2
cis-$C_6Cl_5CCl=CHCl$ (10)	Oil	1590 (C=C)	6.50	27.8	27.3	0.3	0.4	71.9	71.4

[a] The elemental formulas were supported by analysis of the parent and isotope peaks, clearly visible in all cases, in the mass spectra. [b] This compound was only 85% pure (by nmr and mass spectrometry); the impurity could not be removed by recrystallization or preparative gas chromatography.

in the reduction. Initial cleavage of the α C–Cl bond leads to an anion (step 1) which, upon subsequent elimination of chloride from the β position (step 1a), gives a chloroacetylene analogous to the primary product proposed in the electrolytic reduction of hexachlorobutadiene.[3] The chloroacetylene was not observed, apparently because the potential at which it is reduced to the major product 2 (step 2) is more positive than the potential at which the reaction was carried out. Addition of a proton to the initially formed anion (step 1b) results in the formation of the heptachlorostyrene **3**. The lower percentage of **3** formed in runs conducted at higher pH is thus explained. Further reduction of **3** was not observed, though reductive dechlorination at the β position is expected at a sufficiently negative cathode potential.[4,5] That reductive dechlorination did not occur at the β position of **1** points to exclusive formation of an anion adjacent to the pentachlorophenyl group in the initial step of the reduction. The important role of the pentachlorophenyl group in anion stabilization, inferred from chemical reactivity data,[6] is thus supported in the electrolytic reduction. The results are also in accord with the reactivity of octafluorostyrene in hydride reduction which proceeds, presumably through formation of $C_6H_5\bar{C}FCHF_2$, with exclusive substitution at the β position.[7]

Step 3 involves reductive dechlorination at the ring 4 position to give the tetrachloroethynylbenzene **4**, not unexpected in view of the reactivity of this position demonstrated previously with various pentafluorophenyl compounds.[7,8] This step could be minimized by keeping the solution acidic to favor discharge of hydrogen at the cathode. Finally, reduction of **4** (step 4) leads to the tetrachlorostyrene **5**, a major product of deliberate overreduction. Further reduction of **5** was not observed although this might have reasonably been expected. The ease of reduction observed for styrene *vs.* ethynylbenzene[9] is thus reversed for the tetrachloroethynylbenzene **4** and the tetrachlorostyrene **5**. The explanation for this may lie in the steric opposition to further saturation in the side chain from chlorine substituents at the 2 and 6 positions in the pentachlorophenyl ring.[10]

Reduction of heptachloro-2- and -3-vinylpyridines (**6**) followed a course similar to that of **1**, yielding as major product the corresponding tetrachloro-2- and 3-ethynylpyridines (**7**). Both reactions were carried out in 1:1 methanol–dimethoxyethane containing ammonium acetate and aqueous ammonia at a lead cathode, and the products were obtained in crude yields of 63% (**7a**) and 69% (**7b**). Along with **7a** there was isolated small amounts of *trans*-β-3,4,5,6-pentachloro-2-vinylpyridine (**8**) and another unidentified product. The occurrence of **8**, rather than the hexachloro derivative analogous to **3**, suggests a greater reactivity of a β *vs.* a ring chlorine atom in the presumed intermediate 2-$Cl_4PyCH=CCl_2$. Insufficient amounts of the two minor products from **6b** were available for identification, but their glc retention times indicate that they are analogous to those from **6a**.

2-$Cl_4PyCCl=CCl_2$ (**6a**) ⟶ 2-$Cl_4PyC\equiv CH$ (**7a**) + *trans*-2-$Cl_4PyCH=CHCl$ (**8**) + 1 other

3-$Cl_4PyCCl=CCl_2$ (**6b**) ⟶ 3-$Cl_4PyC\equiv CH$ (**7b**) + 2 others

The structure of the heptachlorostyrene by-product **3** rests on the following evidence. Chlorination of pentachloroethynylbenzene (**2**) at room temperature in carbon tetrachloride resulted in the formation of two products, **9** and **10**, both C_8HCl_7 from elemental and mass spectroscopic analysis, in the ratio of 2.5:1. The major product, mp 109–110°, had a single nmr absorption at 6.67 ppm and the minor product, an oil, had a single nmr absorption at 6.50 ppm. They are thus geometric isomers, with the assignment of **9** as *trans*- and **10** as *cis*-α,β,2,3,4,5,6-heptachlorostyrene being favored on their formation ratio and melting point difference. The addition of chlorine to pentafluoroethynylbenzene to give 90% *trans*- and 10% *cis*-1,2-dichloro-1-pentafluoroethylene[11] may be cited to support this argument. Compound **3**, the electrolytic reduction by-product, also C_8HCl_7 by elemental and mass spectroscopic analysis, had mp 108–109° and

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a single nmr absorption, at 6.66 ppm, but was differentiated from **9** by its infrared spectrum and glc retention time. The structure of **3** then corresponds, by elimination of possibilities, to α,β,2,3,4,5,6-heptachlorostyrene.

Experimental Section

General.—Melting points were taken in glass capillaries and are uncorrected. The ir spectra were determined in carbon tetrachloride solution using a Beckman IR-4 spectrophotometer. The nmr spectra were determined in deuteriochloroform using a Varian A-60 spectrophotometer, with TMS as the internal standard. Gas chromatography was carried out using a Varian Aerograph A-90P instrument equipped with a thermal conductivity detector, on a 5 ft × 0.25 in. stainless steel column containing 20% SE-30 on Chromosorb W, at 230°. Perchlorinated styrene and vinylpyridine starting materials were prepared according to a published vapor phase chlorination procedure.[12]

An undivided cell containing as electrodes either alternating plates of sheet lead and graphite or a pool of mercury stirred by a magnetic bar and faced by a graphite disk was used with a calomel reference electrode and an NJE Model RVC-36-25 M potentiostat. In all experiments, oxidation of methanol was the principal anode reaction. Reactant concentrations were 0.1–0.15 mol/l., and electrolyte concentrations were 0.1, 0.5, and 1.0 *M* for hydrochloric acid, ammonium chloride, and ammonium acetate, respectively. Cathode current densities were 0.005–0.02 A/cm² and current efficiencies ranged from 50 to 80% based on a transfer of four electrons per molecule. The cathode potentials were maintained at values corresponding to the least amount of overreduction for a given reaction, as determined by following the course of reaction by glc, and were within the range −0.7 to −1.5 V (*vs.* sce). The cathode was generally partly covered at the end of the reaction by a yellow amorphous film which was not identified.

Reduction of Octachlorostyrene (1).—The following example, corresponding to run 2 of Table I, is illustrative. A mixture of 70.0 g (0.185 mol) of octachlorostyrene, 1 l. of methanol, 1.2 l. of dimethoxyethane, 20 ml of concentrated aqueous ammonia, 150 g of ammonium acetate, and 100 ml of water was warmed to 60° until complete solution was effected and then placed in a cell equipped with alternating plates, three each, of sheet lead (0.2-cm thickness) and graphite (0.5-cm thickness). The gross working lead cathode surface was 470 cm². Electrolysis was carried out with vigorous stirring at a cathode potential of −1.2 V (*vs.* sce) resulting in an average flow of 10-A current, or an average current density of 0.021 A/cm². After 2 hr, glc analysis indicated a conversion of 86% and product distribution as shown in Table I. The reaction solution was drained from the cell and 250 ml of water was added. Overnight cooling resulted in the separation of 26.4 g of pentachloroethynylbenzene (**2**): ir 3280 (≡CH) and 2200 cm⁻¹ (C≡C), mp 180–182° (lit.[6] mp 185–186°). The mother liquor was further diluted with water (3 l.) and extracted with dichloromethane (three 500-ml) portions. Preparative glc of the concentrated extract resulted in the isolation of β,β-2,3,4,5,6-heptachlorostyrene (**3**) and 2,3,-5,6-tetrachloroethynylbenzene (**4**). The properties of these and subsequent products are given in Table II (p 2001).

From a reaction similar to the above, but electrolyzed 4 hr at −1.4 V (*vs.* sce) to favor overreduction, preparative glc of the crude product resulted in the isolation of 2,3,5,6-tetrachlorostyrene (**5**), the major product.

Reduction of Heptachloro-2-vinylpyridine (6a) and Heptachloro-3-vinylpyridine (6b).—Reduction was carried out in essentially the same fashion as described above. The crude product from **6a** contained 50.6% tetrachloro-2-ethynylpyridine (**7a**), isolated in pure form by crystallization from ethanol, 13.0% *trans*-β,3,4,5,6-pentachloro-2-vinylpyridine (**8**), isolated in pure form by preparative glc, 17.6% a third product which was not identified, and 18.8% unreacted **6a**.

The crude product from **6b** contained 50.7% tetrachloro-3-ethynylpyridine (**7b**), isolated in pure form by crystallization from ethanol, 22.4% two other products which were not identified, and 26.9% unreacted **6b**.

Addition of Chlorine to Pentachloroethynylbenzene (2).—Chlorine gas was bubbled through a stirred solution of 10 g (0.04 mol) of **2** in 150 ml of carbon tetrachloride at the rate of *ca.* 10 ml/min. After 30 hr, most of the **2** disappeared and two major products were formed in the ratio of 2.5:1. Evaporation of the solvent gave 14.4 g of an oil which partially solidified on standing. Two recrystallizations from acetone gave 1.5 g of the major component (**9**) as tan crystals. From the concentrated mother liquors, the minor component (**10**) was obtained as a colorless oil by preparative glc.

(12) W. H. Taplin (Dow Chemical Co.), U. S. Patent 3,420,833 (1969).

Registry No.—**1**, 29082-74-4; **3**, 29082-75-5; **4**, 29082-76-6; **5**, 29082-77-7; **6a**, 22652-20-6; **6b**, 29086-34-8; **7a**, 29086-35-9; **7b**, 29086-36-0; **8**, 29086-37-1; **9**, 29086-38-2; **10**, 29086-39-3.

The Hammick Reaction of Methoxypyridine-2-carboxylic Acids with Benzaldehyde. Preparation of Methoxy-2-pyridyl Phenyl Ketones

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The Hammick reaction,[1,2] synthesis of carbinols by thermal decarboxylation of certain heterocyclic carboxylic acids in the presence of carbonyl compounds, has been widely used in the preparation of a number of 2-pyridyl carbinols.[3,4] Thus far the only substituted pyridine-2-carboxylic acids used as substrates in the Hammick reaction have been the methylpyridine acids.[4] The corresponding carbinols have been obtained by thermal decomposition of these acids in benzaldehyde and anisaldehyde in yields ranging from 35 to 53%. In the present study, synthesis of the methoxypyridine-2-carboxylic acids and their thermal decomposition in benzaldehyde are described. In each case two products, the corresponding methoxy-2-pyridyl phenyl carbinol and the methoxypyridine, were obtained. The carbinols were oxidized to the corresponding ketones by chromic acid solution.

Reaction Medium.—In each case, 1 g of the acid was heated with 6 g of benzaldehyde and 6 g of *p*-cymene. The use of *p*-cymene has been found to increase the yield of the Hammick product.[3,4] All the methoxy acids are soluble in this reaction medium above 90° and insoluble at 25°. The highest temperature for the reaction was 175°, the reflux temperature.

General Procedure.—The finely divided acid was added in one portion to the reaction medium. The mixture was stirred under nitrogen and heated below the decarboxylation temperature until a clear solution was obtained. It was then brought up to the reaction temperature and maintained there for the desired period. On cooling overnight, the unreacted acid, if any, was removed by filtration. The solution was then extracted three times with hydrochloric acid (15%) and the acid extracts were washed with petroleum ether.

(1) (a) D. L. Hammick and P. Dyson, *J. Chem. Soc.*, 1724 (1937); (b) D. L. Hammick and P. Dyson, *ibid.*, 809 (1939).

(2) (a) D. L. Hammick and B. R. Brown, *ibid.*, 173 (1949); (b) D. L. Hammick and B. R. Brown, *ibid.*, 659 (1949).

(3) N. Sperber, D. Papa, E. Schwenk, and M. Sherlock, *J. Amer. Chem. Soc.*, **71**, 887 (1949).

(4) N. H. Cantwell and E. V. Brown, *ibid.*, **75**, 1489 (1953).

TABLE I

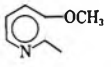
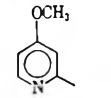
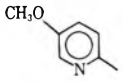
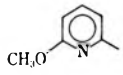
HAMMICK REACTION OF METHOXYPYRIDINE-2-CARBOXYLIC ACIDS IN BENZALDEHYDE AND *p*-CYMENE[a]

Pyridine-2-carboxylic acid	ΔG^*,[b] kcal	Temp, °C	Time, hr	Acid used, g	Acid used, mmol	Carbinol obtained, g	Carbinol obtained, mmol	Methoxypyridine obtained, g	Methoxypyridine obtained, mmol	%[c] carbinol	%[c] methoxypyridine	Ratio of C/M
6-Methoxy-	37.8	174–175	36[d]	10.0	65.4	1.5	7.0	0.6	5.5	10.7	8.4	1.3
6-Methoxy-	37.8	174–175	72[d]	10.0	65.4	2.6	12.2	1.0	9.2	18.6	14.1	1.3
5-Methoxy-	35.9	174–175	12[d]	6.0	39.2	3.8	17.7	1.4	12.8	45.2	32.7	1.4
5-Methoxy-	35.9	174–175	18	6.0	39.2	4.7	21.8	1.7	15.7	55.5	40.2	1.4
4-Methoxy-	32.2	168–170	3	6.0	39.2	4.9	22.7	1.6	14.7	58.0	37.5	1.6
3-Methoxy-	29.0	100–103	2	2.1	13.8	2.0	9.3	0.4	3.7	67.5	27.0	2.5

[a] In 1:6:6 ratio. [b] Reproduced from ref 6. [c] No correction for unreacted acid. [d] Unreacted acid recovered.

TABLE II

PHYSICAL AND SPECTRAL PROPERTIES OF CARBINOLS, $RCHOHC_6H_5$

R =	Registry no.	Mp or bp, °C	Ir[a] (OH), cm^{-1}	Nmr,[b] δ, ppm ($CDCl_3$ solvent)	Mass spectra, m/e (rel intensity)
	29082-98-2	116.5	3600 (v broad, large)	3.7 (s, 3, OCH_3), 5.5 (br, 1, OH); 5.9 (s, 1, CHOH), 7.15 (m, 2, py), 7.35 (s, 5, C_6H_5), 8.2 (m, 1, py)	215 (100), 200 (23), 154 (11), 138 (70), 110 (30), 109 (34), 108 (68), 94 (15), 80 (10)
	29082-99-3	42	3600, 3400	3.7 (s, 3, OCH_3), 5.4 (br, 1, OH), 5.75 (s, 1, CHOH), 6.6–6.9 (m, 2, py), 7.3 (s, 5, C_6H_5), 8.3 (m, 1, py)	215 (100), 214 (47), 198 (11), 138 (45), 109 (44), 108 (17)
	29086-45-1	77	3600, 3400	3.75 (s, 3, OCH_3), 5.0 (br, 1, OH), 5.65 (s, 1, CHOH), 6.9–7.1 (m, 2, py), 7.3 (s, 5, C_6H_5), 8.1 (m, 1, py)	215 (100), 198 (46), 154 (53) 138 (10), 94 (20), 85 (60), 69 (70), 43 (46)
	29083-00-9	160–162 (2 mm)	3600, 3400	3.95 (s, 3, OCH_3), 4.8 (br, 1, OH), 5.7 (s, 1, CHOH), 6.7 (m, 1, py), 7.2–7.7 (m, 8, C_6H_5 and py)	215 (100), 138 (16), 131 (26), 110 (41), 109 (84), 108 (30), 105 (40), 94 (20), 93 (27), 80 (15)

[a] In $CHCl_3$, 2–6% solution. [b] py = pyridine protons; br = broad peak.

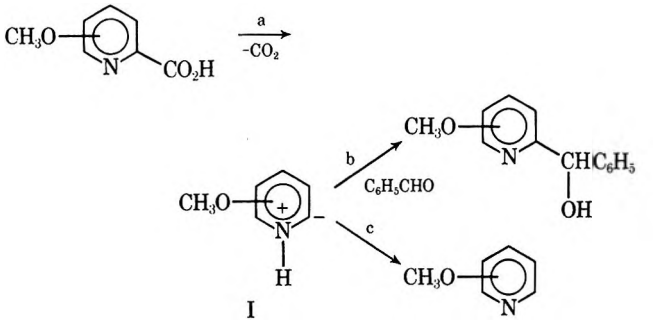
After addition of sodium hydroxide solution (to pH 9), the basic products (methoxypyridine and carbinol) were extracted with ether. After removal of ether, the two products were separated by distillation, the methoxypyridine having a much lower boiling point. In the case of solid carbinols, these were also separated by filtration; the methoxypyridines were removed by washing with water and isolated from the filtrate by ether extraction. The carbinols were converted to the ketones by chromic acid oxidation as described earlier.[5]

Results and Discussion

The results of a few runs are reported in Table I. Over 90% of the acids have been accounted for by the two products except in the case of the 6-methoxy acid. This acid reacts very slowly at 175°, the reaction not being complete even after 72 hr.

The kinetics of decarboxylation of these methoxy acids in *m*-nitrotoluene have been studied by Moser[6] and the free energies of activation, ΔG^* (Table I), were calculated from the rate constants at various temperatures. Decarboxylation was found to be most facile in the case of the 3-methoxy acid (lowest ΔG^*, rate constant at 100.9° = 3.14×10^{-4} sec^{-1})[6] and most difficult in the case of the 6 isomer (highest ΔG^*, rate constant at 200.0° = 0.33×10^{-4} sec^{-1}).[6] As seen in Table I, the 3-methoxy acid gives the highest yield of the carbinol and the 6 isomer the lowest yield.

The formation of the two products may be shown as follows. The slow or rate-determining step a results in the formation of the reactive intermediate I which then

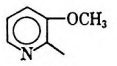
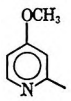
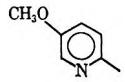
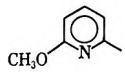


reacts in the subsequent fast or product-determining steps b and c. The product ratio, carbinol to methoxypyridine, reflects the relative rates of steps b and c. This ratio is seen to be increasing with the ease of decarboxylation (lower ΔG^*), being the highest for the 3-methoxy acid. The intermediate I formed at lower temperature is expected to be less energetic (more stable). As the stability of I increases, step b is seen to become faster than step c, resulting in a higher yield of the carbinol.

Step c involves only a proton transfer (known as a fast process), while step b involves reaction of I with benzaldehyde. For step b to be faster than step c, the benzaldehyde molecules (which are in excess) must occupy favorable positions around intermediate I. This may also be visualized as a concerted process.[7]

(5) E. V. Brown and M. B. Shambhu, *Org. Prep. Proced.*, **2**, 285 (1970).
(6) R. Moser, Ph.D. Thesis, University of Kentucky, 1970.
(7) K. Schofield, "Hetero-aromatic Nitrogen Compounds," Plenum Press, New York, N. Y., 1967, pp 163 and 319.

TABLE III
PHYSICAL AND SPECTRAL PROPERTIES OF KETONES, $RCOC_6H_5$

R =	Registry no.	Mp or bp, °C	Ir[a] (C=O), cm^{-1}	Nmr,[b] δ, ppm ($CDCl_3$ solvent)	Calcd for $C_{13}H_{11}NO_2$: C, 73.24; H, 5.17; N, 6.57
	19974-93-7	34–35, 174–175 (3 mm)	1660	3.8 (s, 3, OCH_3), 7.2–7.5 (m, 5, Ar), 7.6–7.8 (m, 2, Ar), 8.1 (m, 1, py)	C, 73.03; H, 4.97; N, 6.47
	29082-95-9	45–46	1640	3.9 (s, 3, OCH_3), 7.0 (m, 1, py), 7.3–7.6 (m, 4, Ar), 8.0–8.2 (m, 2, Ar), 8.5 (m, 1, py)	C, 73.62; H, 5.01; N, 6.42
	29082-96-0	75	1650	3.9 (s, 3, OCH_3), 7.2–7.6 (m, 4, Ar), 8.0–8.2 (m, 3, Ar), 8.4 (m, 1, py)	C, 72.94 H, 5.27; N, 6.22
	29082-97-1	124–127 (2 mm), 40–42	1640	3.9 (s, 3, OCH_3), 6.9 (m, 1, py), 7.3–7.8 (m, 8, Ar)	C, 73.04; H, 4.98; N, 6.32

[a] In $CHCl_3$, 2–6% solution. [b] Py = pyridine protons.

Experimental Section

All melting points are uncorrected and were obtained using the Fisher-Johns melting block. Infrared spectra were recorded with a Beckman IR-8 spectrometer. Nmr spectra were taken on a Varian Model A-60 spectrometer; chemical shifts are reported in parts per million (δ) from TMS as the internal standard. The mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E spectrometer at 70 eV and 200°. The properties of the carbinols and ketones are reported in Tables II and III. The general procedure for the Hammick reaction has already been described.

3-Methoxypyridine-2-carboxylic Acid.—A solution of 6.0 g (0.032 mol) of 2-bromo-3-methoxypyridine[6] in 50 ml of anhydrous ether was added to a solution of *n*-butyllithium (0.06 mol) in 50 ml of ether at −40 to −50° over a period of 30 min. The resulting red mixture was stirred for 15 min below −40° and then poured into a slurry of excess Dry Ice in 200 ml of ether. After standing overnight, the ethereal slurry was extracted with 50 ml of water. The aqueous extract was washed twice with 20 ml of benzene, the benzene extracts being discarded. The aqueous solution was made acidic (pH 4) by the addition of 48% hydrobromic acid solution. A saturated solution of copper sulfate was added. After cooling in an ice bath, the grey precipitate of the copper salt was removed by filtration and washed with two 5-ml portions of cold water. The copper salt was then suspended in 50 ml of water and copper sulfide was precipitated by bubbling hydrogen sulfide through the warm solution. After removal of copper sulfide by filtration, the filtrate was evaporated to dryness at room temperature. The crude acid (2.8 g) was recrystallized from methanol (1.8 g, 37%): mp 130° (rapid decomposition); nmr (DMSO-d_6) δ 3.85 (s, 3, OCH_3), 7.41–7.55 (m, 2, pyridine-4 and -5 protons), 8.18 (m, 1, pyridine-6 proton), and 11.4 ppm (broad, 1, COOH).

Anal. Calcd for $C_7H_7NO_3$: C, 54.92; H, 4.57; N, 9.15. Found: C, 54.61; H, 4.65; N, 8.96.

4-Methoxypyridine-2-carboxylic Acid.—To a solution of 3.2 g (0.14 g-atom) of sodium in 150 ml of methanol, 4-nitropyridine-2-carboxylic acid[8] (5.0 g, 0.030 mol) was added. The mixture was refluxed for 2 hr and the methanol was removed by distillation. The residue was treated with hydrochloric acid until pH 3 was attained. The methoxy acid (3.9 g, 85%) was obtained *via* the copper salt as colorless crystals: mp 204° dec; nmr (DMSO-d_6) δ 3.95 (s, 3, OCH_3), 7.3 (m, 2, pyridine protons), 8.1 (m, 1, pyridine proton), and 11.2 ppm (broad, 1, COOH).

Anal. Calcd for $C_7H_7NO_3$: C, 54.92; H, 4.57; N, 9.15. Found: C, 54.61; H, 4.51; N, 9.06.

5-Methoxypyridine-2-carboxylic Acid.—To a solution of 12.3 g (0.1 mol) of 5-methoxy-2-methylpyridine[9] in 350 ml of water, 70 g (0.44 mol) of potassium permanganate was added in ten portions over 3 hr. The mixture was vigorously stirred and maintained at 90–95°. The hot mixture was filtered and the filtrate was made acidic (pH 4) by addition of hydrochloric acid after cooling. The acid (7.2 g, 47%) was isolated *via* the copper salt: mp 167°; nmr ($CDCl_3$) δ 3.85 (s, 3, OCH_3), 7.4–7.9 (m, 2, pyridine protons), 8.3 (m, 1, pyridine protons), and 9.8 ppm (broad, 1, COOH).

Anal. Calcd for $C_7H_7NO_3$: C, 54.92; H, 4.57; N, 9.15. Found: C, 54.62; H, 4.49; N, 9.08.

6-Methoxypyridine-2-carboxylic Acid.—To a solution of 6 g (0.26 g-atom) of sodium in 150 ml of methanol, 11 g (0.054 mol) of 6-bromopyridine-2-carboxylic acid[10] (made by the oxidation of 6-bromo-2-methylpyridine[11] using potassium permanganate) was added. The mixture was refluxed for 6 hr and the methanol was removed by distillation. To the residue 100 ml of water was added and the aqueous solution was made acidic (pH 2) by hydrochloric acid. The methoxy acid was removed by filtration (7 g, 84%): mp 129–130°; nmr ($CDCl_3$) δ 4.0 (s, 3, OCH_3), 7.0 (m, 1, pyridine-4 proton), 7.8 (m, 2, pyridine protons), and 9.2 ppm (broad, 1, COOH).

Anal. Calcd for $C_7H_7NO_3$: C, 5.492; H, 4.57; N, 9.15. Found: C, 54.67; H, 4.44; N, 9.21.

Registry No.—Benzaldehyde, 100-52-7; 3-methoxypyridine-2-carboxylic acid, 16478-52-7; 4-methoxypyridine-2-carboxylic acid, 29082-91-5; 5-methoxypyridine-2-carboxylic acid, 29082-92-6; 6-methoxypyridine-2-carboxylic acid, 26893-73-2.

(8) E. V. Brown, *J. Amer. Chem. Soc.*, **76**, 3167 (1954).
(9) L. Marion and W. F. Cockburn, *ibid.*, **71**, 3403 (1949).
(10) H. Gilman and S. M. Spatz, *J. Org. Chem.*, **16**, 1485 (1951).
(11) H. P. T. Willink, Jr., and J. P. Wilbaut, *Recl. Trav. Chim. Pays-Bas*, **53**, 417 (1934).

Improved Preparation of 6-Methoxybenzoxazolinone[1]

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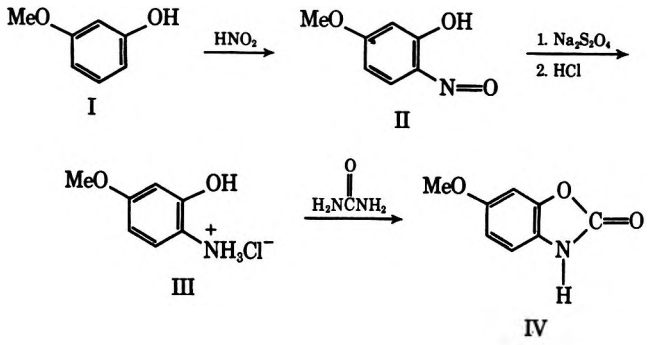
Received December 18, 1970

6-Methoxybenzoxazolinone (IV) has been implicated as a natural factor for the resistance of corn (*Zea mays L.*) to disease and insect attack.[2,3] To evaluate the role of IV as a disease resistance factor in Helmin-

(1) Mention of a trademark name, proprietary product, or specific equipment does not constitute a guarantee or warranty by the U. S. Department of Agriculture, and does not imply its approval to the exclusion of other products that may also be suitable.
(2) A. Stoessl in "Recent Advances in Phytochemistry," Vol. III, C. Steelink and V. C. Runeckles, Ed., Appleton-Century-Crofts, New York, N. Y., 1970.
(3) S. D. Beck, *Ann. Rev. Entomol.*, **10**, 207 (1965).

thosporium leaf blight of corn, we attempted to synthesize this compound according to reported methods.[4-6] These methods gave very low yields. One of the procedures was hazardous because phosgene was used.[5]

A shorter method with higher yield was developed. The first objective was to prepare the immediate precursor of IV, 2-amino-5-methoxyphenol hydrochloride (III), in high yield with a minimum number of steps. The orthoaminophenol obtained by reducing 2-nitroso-5-methoxyphenol (II) was not isolated. To



I II III IV

maximize the yield of III, neutralization of the reducing solution and other steps including the urea fusion were carried out in the dark or with photographic safety lights. Separatory funnels and flasks were flushed with N_2 gas. The uv, ir, melting point, and derivative data for IV were in good agreement with the literature values.[4-7]

Preparations of the amine hydrochloride which were black, blue, green, purple, or red reduced the yields of IV. Apparently some of the colored substances were partial oxidation products known as Wurster's salts.[8] Usually the white amine hydrochloride samples became grayish white and then blue. These blue preparations were fused with urea to yield about 17% IV when calculated on the basis of the initial starting material, *m*-methoxyphenol (I). This overall yield was about 60 times as great as the yield which we obtained by the use of the method of Klun and Brindley.[6]

Experimental Section[9]

2-Nitroso-5-methoxyphenol (II).—This compound was prepared in yields of 87–93% by the procedure of Hodgson and Clay.[10] The reaction mixture was held at 4° in the dark for 24 hr and the precipitate was isolated by filtration.

Preparation of 2-Amino-5-methoxyphenol Hydrochloride (III) for Fusion with Urea.—2-Nitroso-5-methoxyphenol (5.37 g) was suspended in 300 ml of water. Solid sodium hydrosulfite (18.5 g) was added slowly with continuous rapid stirring.[6,11] The reducing solution (bright yellow) was heated at 50–60° for 15 min, cooled, and neutralized to pH 6 with a saturated aqueous solution of $NaHCO_3$ added slowly by the drop with very rapid stirring. 2-Amino-5-methoxyphenol was extracted from the reducing solution (pH 6) with peroxide-free diethyl ether (eight 100-ml portions). The ether extract was passed through anhydrous Na_2SO_4. The 250-ml round-bottom flask containing the dry ethereal solution of the aminophenol was gently agitated and flushed with dry HCl gas for 1 min. The amine hydrochloride precipitated immediately as a white solid which became gray-white and then blue if water and O_2 were present. The ether was removed by rotatory evaporation *in vacuo* at 20°. The dry amine hydrochloride was mixed with urea (6 g) in a flask fitted with an air condenser, and heated in an oil bath at 170–180° for 2.5 hr.[4] Owing to its extreme instability, the orthoaminophenol was converted without delay to the hydrochloride. Highest yields were obtained when the amine hydrochloride was prepared and fused with urea as a continuous operation in the same flask in the absence of water.

Isolation of 6-Methoxybenzoxazolinone (IV) from the Fusion Mixture.—The fusion mixture was washed with 1.2 *N* HCl. The remaining residue was dissolved in ethyl alcohol, and about 50 ml of 1.2 *N* HCl was added. The alcohol was removed by rotatory evaporation *in vacuo* at 28°. The product (IV) was isolated from the acidic aqueous solutions by continuous extraction with diethyl ether. The wet ether was removed, and the residues were dissolved in a minimum amount of warm dry ether. The ethereal solution of crude IV was loaded on a silica gel (Adsorbosil-1) column which had been pressure packed in diethyl ether–petroleum ether (75:25 v/v) (EPE). The column was developed with EPE under low N_2 pressure and 5-ml fractions were collected (1 ml/min). IV was the first major compound to be eluted from the column and was detected in the fractions by thin layer chromatography on silica gel (microscope slides) developed with EPE (R_f 0.58). All compounds appeared as yellow spots on a purple background when the plates were sprayed with 3% aqueous $KMnO_4$. Fractions containing IV were combined and the solvent was removed. The light pink solid was decolorized with activated charcoal and recrystallized in water to give colorless needles: mp 154–155° (lit.[4] mp 154–155°); uv max (absolute EtOH) 231 mμ (ε 9138), 291 (5230); uv max (water) 230 mμ (ε 10,000), 286 (5380) [lit.[12] uv max (water) 230 mμ (ε 10,000), 287 (4500); lit.[5] uv max (water) 285–286 mμ (ε 5500)]; ir (KBr) 1326 (C—N stretching in Ar-NHR), 1498 (N—H bending, amide II band), 1620 (C=C aromatic skeletal in plane vibr), 1787 (C=O stretching, carbamate), 3330–3060 cm^{-1} (N—H stretching, multiple amide I band); mass spectrum (70 eV) *m/e* (rel intensity) M + 165.0428 (100%), calcd for $C_8H_7O_3N$ 165.0426. The ir and uv spectra were primarily the same as those reported in the literature.[6,7]

Anal. Calcd for $C_8H_7O_3N$: C, 58.18; H, 4.27; N, 8.48. Found: C, 57.96; H, 4.28; N, 8.42.

The benzimide was prepared: mp 165–167° (lit.[4] mp 163–164°); mass spectrum (70 eV) *m/e* (rel intensity) M + 269.0669 (14%), calcd for $C_{15}H_{11}O_4N$ 269.0688.

Registry No.—IV, 532-91-2.

Acknowledgment.—We thank Dr. J. M. Ruth, Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture, Beltsville, Md., for making mass measurements.

(4) E. E. Smissman, J. B. LaPidus, and S. D. Beck, *J. Amer. Chem. Soc.*, **79**, 4697 (1957).

(5) P. K. Hietala and O. Wahlroos, *Acta Chem. Scand.*, **10**, 1196 (1956).

(6) J. A. Klun and T. A. Brindley, *J. Econ. Entomol.*, **59**, 711 (1966).

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(8) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Oxford University Press, Oxford, 1942, p 97.

(9) Melting points were determined by hot stage microscopy and uncorrected. Mass spectra were measured on a CEC Model 21-110B instrument. Infrared and ultraviolet spectra were recorded, respectively, on Perkin-Elmer Model 621 and Cary Model 15 instruments.

(10) H. H. Hodgson and H. Clay, *J. Chem. Soc.*, 2775 (1929).

(11) H. E. Gahagan and R. O. Mumma, *Phytochemistry*, **6**, 1441 (1967).

(12) E. E. Smissman, J. B. LaPidus, and S. D. Beck, *J. Org. Chem.*, **22**, 220 (1957).

The Mechanism of Formation of Pentaazadecanetetraones in the Reaction of Aryl Isocyanates with *N,N*-Dimethylformamide

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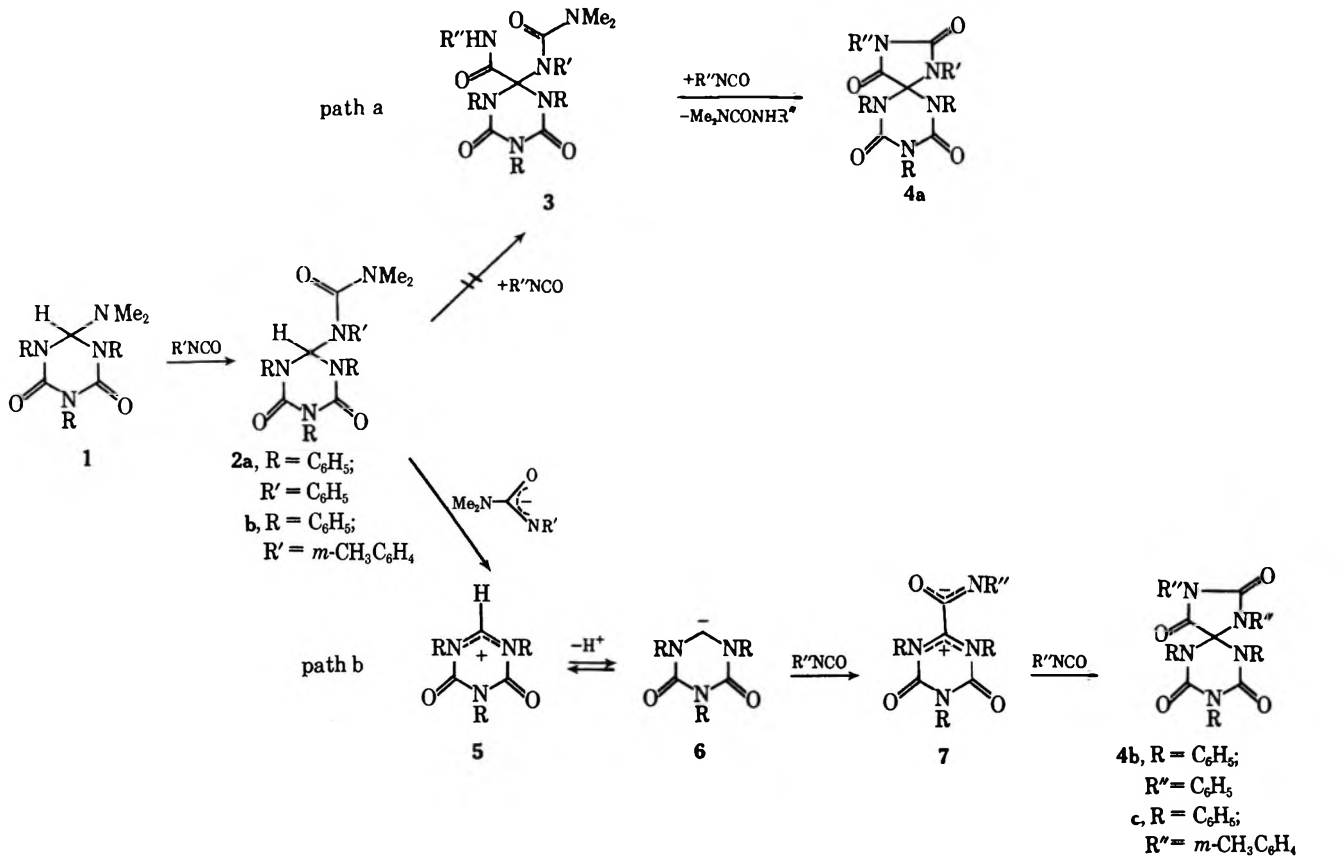
Received December 3, 1970

The reaction of aryl isocyanates with *N,N*-dimethylformamide gives *N*-dimethyl-*N'*-arylformamidines[1]

(1) M. L. Weiner, *J. Org. Chem.*, **25**, 2245 (1960).

SCHEME I



which undergo further reaction with aryl isocyanates to yield heterocyclic 2:1 adducts **1**, 3:1 adducts **2**, and spiro compounds **4**.[2-5]

The formation of the ureido-*s*-triazine derivative **2** from its precursor **1** is readily explained by an "insertion reaction" of the heterocumulene into the exocyclic CN single bond in **1**.[6] For the formation of **4**, however, several mechanisms could be visualized. Addition of a second isocyanate molecule to **2**, either by an insertion into the CH bond, as proposed by Dyer, *et al.* (path a, Scheme I), or by a repeated insertion into the exocyclic CN bond could lead to cyclization with formation of **4**. In contrast, an elimination sequence (path b, Scheme I) could give rise to the formation of the heterocarbene intermediate **6**, which would undergo further reaction with two isocyanate molecules to produce **4**. In order to differentiate between an addition (a) and an elimination (b) mechanism, we investigated the reaction of **1** and **2** with different aromatic isocyanates.

In case of an addition sequence a mixed spiro compound **4a** is expected, having one original aryl group (R′) and the new aryl group (R″) attached to the five-membered ring portion of the molecule. In contrast, the elimination sequence would result in the formation of a spiro compound **4b** having two new aryl groups (R″) incorporated into the molecule.

The reaction of **1** (R = C_6H_5) with phenyl isocyanate, following a procedure by Dyer, *et al.*,[4] gives the ureido-*s*-triazinedione **2a** (R = R′ = C_6H_5). By treating **1** with *m*-tolyl isocyanate under similar conditions, the corresponding **2b** (R = C_6H_5; R′ = *m*-$CH_3C_6H_5$) is obtained. Heating of both ureido-*s*-triazinediones **2a,b** with excess phenyl isocyanate at 150° gives exclusively the spiro compound **4b** (R = R″ = C_6H_5), identical with **4b** prepared from **1** and phenyl isocyanate. On treatment of **2a** with excess *m*-tolyl isocyanate at 150° the spiro compound **4c** (R = C_6H_5; R″ = *m*-$CH_3C_6H_4$) is formed exclusively, thus proving that in both cases the aryl moiety in the acyclic urea group in **2** is being eliminated. Of course, heating **2b** with excess *m*-tolyl isocyanate also affords **4c**.

A mechanism consistent with the observed facts is shown in Scheme I (b). Elimination of an urea anion in **2** gives **5**, which loses a proton to yield the heterocarbene **6**. Reaction of **6** with aryl isocyanate affords, *via* a delocalized zwitterion **7**, the spiro compound **4b** and **c**.

Heating of **2a** in the absence of aryl isocyanate to 330–340° and under constant removal of volatile decomposition products caused the formation of a solid material, mp >360°, analyzing for $C_{42}H_{30}N_6O_4$. The molecular weight of 682, determined by mass spectroscopy, indicates that the compound may be the dimer **8** of the heterocarbene **6**. Dyer, *et al.*,[4] found also that thermal decomposition of **4b** at 330–360° yields besides 2 mol of phenyl isocyanate a colorless high melting solid which we found to be identical with **8** (by comparison of ir and nmr spectra). Pyrolysis of **4c** also gave only **8**, thus indicating that the imidazolinedione rather than the *s*-triazine ring is cleaved in this reaction.

(2) R. Richter, *Chem. Ber.*, **101**, 3002 (1968).

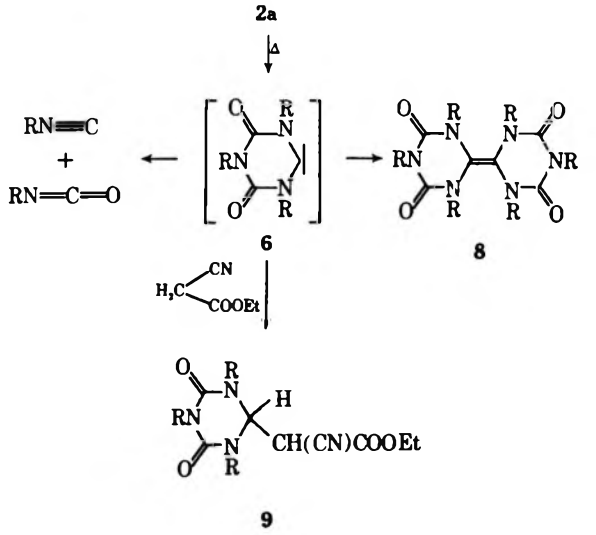
(3) H. Ulrich, B. Tucker, F. A. Stuber, and A. A. R. Sayigh, *J. Org. Chem.*, **33**, 3928 (1968).

(4) E. Dyer, T. E. Majewski, and J. D. Travis, *ibid.*, **33**, 3931 (1968).

(5) For a discussion of the cycloaddition reaction of imines with heterocumulenes, see R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **8**, 312 (1969); R. Huisgen, *ibid.*, **7**, 321 (1968); and H. Ulrich and R. Richter in "Newer Methods of Preparative Organic Chemistry," Vol. 6, Verlag Chemie, Weinheim/Bergstr., Germany, 1970.

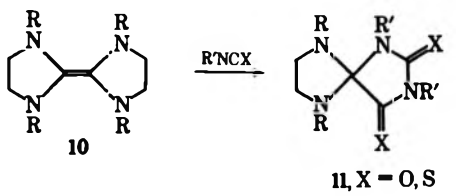
(6) For similar reactions, see H. Ulrich and A. A. R. Sayigh, *Angew. Chem., Int. Ed. Engl.*, **5**, 844 (1966).

(The presence of *m*-tolyl groups in **8** could have been easily detected by nmr spectroscopy.) The characteristic odor of isonitriles was also noted in the volatile decomposition products indicating some degradation of **6** into isonitrile and isocyanate. The ir spectrum of **8** (KBr) shows two strong bands of almost equal intensity in the double bond region at 1710 and 1745 cm^{-1}. Similar ir absorptions (1696 and 1731 cm^{-1} in dioxane) were observed for the methyl homolog of **8**, previously obtained by Piskala[7] upon pyrolysis of 2-methoxy-1,3,5-trimethyltriazine-4,6-dione. Attempts to oxidize **8** to triphenyl isocyanurate (with H_2O_2-formic acid, peracetic acid, potassium permanganate in pyridine or acetic acid) were unsucessful; only unreacted starting material was recovered. Insertion of the heterocarbene



intermediate **6** into a carbon–hydrogen bond was observed in the reaction of **2a** with ethyl cyanoacetate. Thus heating of **2a** with ethyl cyanoacetate at 140–145° for 1 hr yields the insertion product **9**.

The further reaction of the heterocarbene **6** with isocyanate to produce **4**, as outlined in Scheme I, is quite similar to the reaction of bis(1,3-diphenylimidazolinylidene-2) (**10**) with isocyanates or isothiocyanates, which yields the spiro compound **11**.[8,9]



The dimer **8** in contrast to **10** does not undergo a reverse reaction with aryl isocyanates (*via* the monomer) as evidenced by the fact that refluxing of **8** with excess phenyl or *p*-chlorophenyl isocyanate for 24 hr resulted in complete recovery of the starting material.

(7) A. Piskala, *Tetrahedron Lett.*, 2587 (1964); A. Piskala and J. Gut, *Collect. Czech. Chem. Commun.*, **29**, 2794 (1964).

(8) H. E. Winberg and D. D. Coffman, *J. Amer. Chem. Soc.*, **87**, 2776 (1965).

(9) M. Regitz and J. Hocker, *Synthesis*, 301 (1970).

Experimental Section[10]

2-[1-(1-*m*-Tolyl-3,3-dimethylureido)]-1,3,5-triphenylhexahydro-1,3,5-triazine-4,6-dione (2b).—A mixture of 5.0 g (0.013 mol) of 2-dimethylamino-1,3,5-triphenylhexahydro-1,3,5-triazine-4,6-dione (**1**) and 25.0 g (0.19 mol) of *m*-tolyl isocyanate was kept at 80–85° for 16 hr. On cooling colorless crystals separated from the reaction solution. Filtration and thorough washing with ether left 3.70 g (53%), mp 205°. Recrystallization from acetone–ether gave tiny white needles: mp 207–210°; ir (KBr) 1715, 1670, 1650 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.15 (s, 3, CH_3C), 2.4 (s, 6, $(CH_3)_2N$), 6.30–6.50 (m, 2, aromatic), 6.8–7.6 (m, 18, aromatic and CH).

Anal. Calcd for $C_{31}H_{29}N_5O_3$: C, 71.66; H, 5.63; N, 13.48. Found: C, 71.63; H, 5.62; N, 13.22.

1,3,6,8,10-Pentaphenyl-1,3,6,8,10-pentaazaspiro[4.5]decane-2,4,7,9-tetraone (4b).—A mixture of 1.0 g (0.0019 mol) of **2b** and 7.0 ml of phenyl isocyanate was kept for 2 hr at 150°. After the reaction the excess isocyanate is removed by vacuum distillation and the residue is treated with ether. This was allowed to stand at room temperature; 0.93 g (81%) of **4b** separated in colorless crystals, mp 228–234°. A mixture with authentic **4b** (prepared according to *loc. cit.*[3,4]) did not give a melting point depression; the material is identical in ir and nmr with authentic **4b**.

1,3-Di-*m*-tolyl-6,8,10-triphenyl-1,3,6,8,10-pentaazaspiro[4.5]decane-2,4,7,9-tetraone (4c). A. From 2b and *m*-Tolyl Isocyanate.—A mixture of 1.0 g (0.0019 mol) of **2b** and 6.0 g (0.045 mol) of *m*-tolyl isocyanate was treated as described above for the preparation of **4b** yielding 1.0 g (78%) of **4c**: mp 270–273°, after recrystallization from chloroform–ether; ir (KBr) 1790, 1725, 1695 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.2–7.6 (m, 23, aromatic protons), 2.42 (s, 3, CH_3), 2.2 (s, 3, CH_3).

Anal. Calcd for $C_{37}H_{29}N_5O_4$: C, 73.13; H, 4.81; N, 11.53. Found: C, 72.87; H, 4.64; N, 11.34.

B. From 2a and *m*-Tolyl Isocyanate.—A mixture of 5.0 g (0.01 mol) of **2a** and 25 g (0.19 mol) of *m*-tolyl isocyanate was kept for 3 hr at 145–150°. Work-up as described above gave 5.3 g (87%), mp 270–272°, identical in comparison (ir, nmr, mixture melting point) with **4c** prepared under A.

1,1′,3,3′,5,5′-Hexaphenyl[$\Delta^{2,2'(1H,1'H)}$-bis-s-triazine]-4,4′,6,6′-(3*H*,3′*H*,5*H*,5′*H*)-tetraone (8). A. From 2a.—A sample of 1.5 g (0.003 mol) of **2a** was placed into a preheated salt bath and kept at 330–340° for 7 min. During the reaction a liquid product was distilled off under reduced pressure (20–30 mm), which on standing solidified partly: 0.32 g; ir (in $CHCl_3$) and nmr ($CDCl_3$) indicated the presence of *N*,*N*-dimethyl-*N*′-phenylurea; no ir bands in the 2000–2500-cm^{-1} region, indicating the absence of isocyanate or isonitrile. The dark brown residue was taken up in acetone, leaving 0.05 g (5%) of **8** undissolved, creamy crystals, mp >360°. A sample was recrystallized for analysis from DMF: ir (KBr) 1740, 1710 cm^{-1} (C=O); nmr (DMSO-d_6) δ 7.36 (s, C_6H_5), 7.46 (s, C_6H_5).

Anal. Calcd for $C_{42}H_{30}N_6O_4$: C, 73.89; H, 4.43; N, 12.31; mol wt, 682. Found: C, 73.70; H, 4.58; N, 12.13; mol wt, 682 (from mass spectral data).

The material is identical (ir) with a sample prepared from **4b** following the procedure of Dyer, *et al.*[4]

B. From 4c.—A sample of 5.0 g (0.008 mol) **4c** was kept for 25 min in a preheated salt bath at 345–350°. Under reduced pressure (20–30 mm) 1.90 g of a yellowish liquid was distilled off [ir ($CHCl_3$) 2220 cm^{-1} (N=C=O)]. The residue was taken up in acetone and the undissolved colorless crystals were filtered off, 0.45 g (16%), mp >360°. The material is identical (ir) with a sample prepared under A.

[2-(1,3,5-Triphenyl-4,6-dioxohexahydro-s-triazinyl)]ethyl Cyanoacetate (9).—A mixture of 3.0 g (0.006 mol) of **2a** and 5.0 g (0.048 mol) of ethyl cyanoacetate was kept at 140–145°. After 1 hr the formed clear solution was diluted with ether and kept at room temperature overnight. The formed crystals were filtered off and washed with ether leaving 2.1 g (78%) of **9**: mp 175–179°, after recrystallization from acetone–water; nmr ($CDCl_3$) δ 7.35–7.70 (m, 15, C_6H_5), 6.2 (d, 1, tertiary proton on triazine), 3.98 (d, 1, –CH(CN)COOEt), 3.75 (q, 2, CH_2), 1.0 (t, 3, CH_3).

(10) Elemental analyses were by Galbraith Laboratories, Knoxville, Tenn.; ir spectra were taken on a Perkin-Elmer Model 21 spectrophotometer, nmr spectra on a Varian T-60 spectrometer with TMS as internal standard, and mass spectra on a CH-4 mass spectrograph. All melting points (uncorrected) were determined on a Fisher-Johns apparatus.

Anal. Calcd for $C_{28}H_{22}N_4O_4$: C, 68.71; H, 4.88; N, 12.33. Found: C, 68.86; H, 4.99; N, 12.43.

On concentration of the ethereal filtrate 0.4 g (41%) of *N*,*N*-dimethyl-*N'*-phenylurea, mp 134°, was obtained.

Registry No.—**2b**, 29411-17-4; **4b**, 17350-46-8; **4c**, 29411-19-6; **8** (R = Ph), 29411-20-9; **9** (R = Ph), 29520-61-4; *N*,*N*-dimethylformamide, 68-12-2.

Studies of Hydrazine Derivatives. II.[1] The Formation of 1-Phenyl-3-benzoyltriazene by the Base-Catalyzed Condensation of Nitrosobenzene with Benzhydrazide

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Received December 7, 1970

Aromatic nitroso compounds are well known to undergo condensation reactions analogous to those of carbonyl compounds. However, nitrosobenzene (**1**) reacted with a monosubstituted or unsymmetrically disubstituted hydrazine to give a triazene *N*-oxide,[2] and attempted triazene formation in reactions of nitroso compounds with hydrazines have been unsuccessful.[3] In this paper we wish to describe the formation of 1-phenyl-3-benzoyltriazene (**2**) by the base-catalyzed condensation of **1** with benzhydrazide (**3**).

Compound **2** has previously been prepared by the reaction of phenylmagnesium bromide with benzoyl azide.[4]

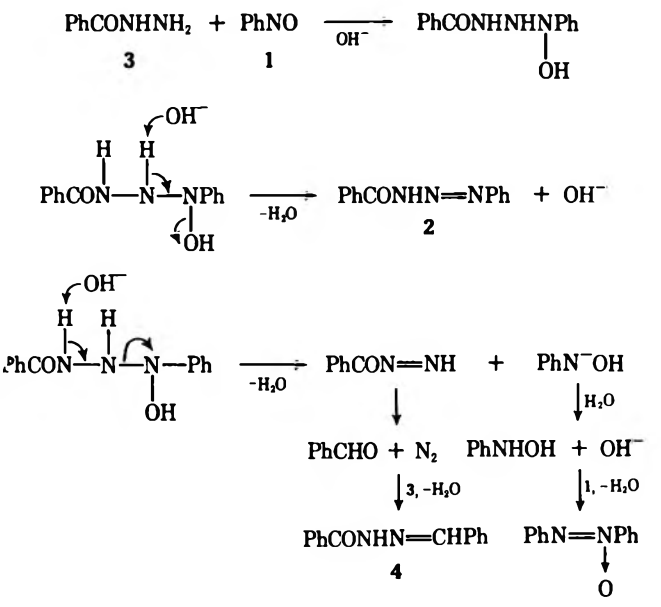
When powdered **1** was added to an aqueous solution of equimolar amounts of **3** and potassium hydroxide at 45–50° with vigorous stirring, a brown oil separated and nitrogen was evolved. After being extracted with ether, compound **2** was separated from the aqueous layer as the silver complex (25%). Benzaldehyde benzoylhydrazone (**4**, 9%), azoxybenzene (24%), benzoic acid (14%), and aniline (4%) were also obtained along with phenyl azide (0.1%) and azobenzene (trace). Either increase or decrease of alkali in the reaction reduced the yield of **2**. Attempted reactions between **1** and **3** in water with sulfuric acid, in *tert*-butyl alcohol with sodium *tert*-butoxide, and in acetic acid did not afford **2** to a significant extent.

As chromatographic treatment on silica gel or alumina brought about the decomposition of **2**, this product could not be obtained quantitatively from the reaction mixture by this technique.

When **2** was treated with dimethylaniline in acetic acid, in hydrochloric acid, or on silica gel in *n*-hexane, *p*-dimethylaminoazobenzene was obtained in 82–84% yield. A diazoaminobenzene-type rearrangement must take place in this process. A solution of the reaction mixture (after being extracted) and dimethylaniline in *n*-hexane was refluxed with a small amount of silica gel for 1 hr and then chromatographed to give *p*-dimethylaminoazobenzene (13%).

The sources of the hydrazone **4** and of azoxybenzene are suggested in Scheme I. Curtius[5] reported that **4** was formed by heating benzhydrazide with alkali, but we were unable to obtain **4** under these conditions in the absence of nitrosobenzene. The formation of aniline was observed by Minato, *et al.*,[6] in the reaction of **1** with hydrazine, though the mechanism has not been well established.

SCHEME I



Experimental Section[7]

Reaction of Nitrosobenzene (1) with Benzhydrazide (3).—To a vigorously stirred solution of 6.8 g (50 mmol) of **3** and 3.2 g (*ca.* 50 mmol) of potassium hydroxide in 75 ml of water was added, over a period of 30 min, 5.4 g (50 mmol) of powdered **1** at 45–50°. The reaction mixture was kept at this temperature for an additional 30 min with stirring. During the reaction, a brown oil separated and gas evolved. The reaction mixture was then cooled, extracted with ether, and separated to an ether layer (a), a water layer (b), and an insoluble solid (c, 1.0 g). The ether layer (a) was washed with aqueous KOH and then with water, dried (Na_2SO_4), and concentrated giving 3.1 g of an oily brown liquid, containing azoxybenzene (2.38 g, 12 mmol, 24%), aniline (0.19 g, 2 mmol, 4%), phenyl azide (0.006 g, 0.05 mmol, 0.1%), and azobenzene (trace), determined by means of column chromatography, vpc, ir, and/or tlc.

The water layer (b), when combined with washings of the ether extract of the reaction mixture, was acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was washed with water, dried (Na_2SO_4), and concentrated giving 4.6 g of a brown viscous residue (b'), containing benzoic acid (0.86 g, 7 mmol, 14%) as the methyl ester, determined by means of vpc. Addition of an alcoholic solution of silver nitrate to the ethanol solution of b' caused precipitation of yellow 1-phenyl-3-benzoyltriazenatosilver (4.15 g, 12.5 mmol, 25%); its ir spectrum was identical with that of an authentic sample.[4] Chromatographic treatment of b' on silica gel or alumina brought about the decomposition of **2**; by the use of a short column (silica

(1) Part I of this series: S. Ito and T. Narusawa, *Bull. Chem. Soc. Jap.*, **43**, 2257 (1970).

(2) (a) O. Fischer and L. Wacker, *Ber.*, **22**, 622 (1889); (b) E. Bamberger and A. Stiegelmann, *ibid.*, **33**, 3554 (1899); (c) O. Fischer and W. Johannes, *J. Prakt. Chem.*, **92**, 60 (1915).

(3) For a review about reactions of aromatic nitroso compounds, see J. H. Boyer in "The Chemistry of the Nitro and Nitroso Groups," H. Feuer, Ed., Interscience, New York, N. Y., 1969, pp 215–299.

(4) A. Bertho, *J. Prakt. Chem.*, **116**, 101 (1927).

(5) T. Curtius, *Ber.*, **33**, 2560 (1900).

(6) H. Minato and T. Fujisawa, *Bull. Chem. Soc. Jap.*, **39**, 1054 (1966).

(7) Melting points were determined in capillary and are uncorrected. The yields of the products are shown in mole percentage based on **1** or **3** used. For the ir spectroscopic determination, a Nihon-Bunko Model DS-301 spectrometer and a Shimadzu gas chromatograph Model GC-2C for the vpc analysis were employed.

gel), only a small amount of 1-phenyl-3-benzoyltriazene (2) was obtained. After recrystallization from *n*-hexane, it melted at 83–84° dec (lit.[4] mp 84° dec). Its ir spectrum was identical with that of an authentic sample.

The ir spectrum of the insoluble solid (c) was identical with that of authentic benzaldehyde benzoylhydrazone (4); recrystallization of c from methanol gave 4, mp 204–205° (lit. mp 204–205°). When c was considered pure, the yield of 4 was 4.5 mmol (9%).

Registry No.—1, 586-96-9; 2, 29411-28-7; 3, 613-94-5.

The Cyclization Reaction of Alkylthiomercaptoenethioamide with Carbonyl Compounds

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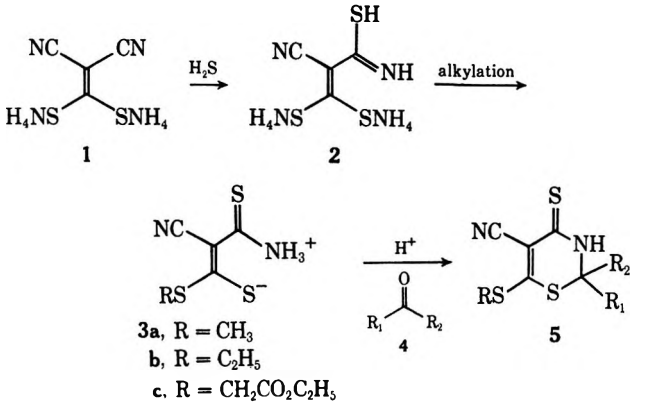
In the course of the investigation of the behavior of enedithiol compounds,[1,2] the reaction of the alkylthiomercaptoenethioamide compound has been studied.

It has been found that 2,2-disubstituted 5-cyano-6-alkylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione (**5**) type compounds could be isolated from the reaction of an alkylthiomercaptoenethioamide, such as 3-alkylthio-3-mercapto-2-cyanothioacrylamide (**3**), with a variety of carbonyl compounds in acidic medium. The derivatives



of 4*H*-1,3-thiazine-4-thione have heretofore not been isolated, although there have been many reports on the preparation of 2*H*-1,3-thiazine-2-thione derivatives[3–6] and 6*H*-1,3-thiazine-6-thione derivatives.[7–10]

Compound **3** was obtained from bisammonium 2,2-dicyanoethenedithiol (**1**) with hydrogen sulfide followed by alkylation of the intermediate 3,3-bis(ammoniumthio)-2-cyanothioacrylamide (**2**). A zwitterion structure was assigned to compound **3a** on the basis of the nmr spectrum (a broad peak at δ 5.00 is characteristic for NH_3^+ group). Compound **5** was obtained in the form of yellow crystals from the reaction of compound **3** and a carbonyl compound **4** by refluxing in alcohol in the presence of sulfuric acid. The physical data of the new compounds are summarized in Table I.

The structure of 2,2-disubstituted 5-cyano-6-alkylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione was established on the basis of spectroscopic evidence together with elemental analyses (see Table II). Thus the ir spectrum revealed the presence of an amino (3120 cm^{-1}) and conjugated cyano (2210 cm^{-1}) group. The nmr spectrum showed the presence of an NH group (a broad peak at *ca.* δ 10.60). The presence of NH was also seen by its effect on the neighboring proton of the R_1 group, causing a split (J = *ca.* 1 Hz). The mass spectrum of **5** showed a characteristic fragment at the mass number of 126, which was considered to be a fragment of the (M − SR − NHR_1R_2) ion (see Table III). The uv spectrum of **5** showed several characteristic absorptions (see Table IV).

Compounds **5** synthesized by the present method were 5-cyano-6-methylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione-2-spirocyclohexane (**5a**), 2,2-dimethyl-5-cyano-6-methylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione (**5b**), 2-methyl-5-cyano-6-methylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione (**5c**), 2-phenyl-5-cyano-6-methylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione (**5d**), 2-furyl-5-cyano-6-methylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione (**5e**), 5-cyano-6-ethylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione-2-spirocyclopentane (**5f**), 2-ethyl-2-methyl-5-cyano-6-ethylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione (**5g**), 2-(3′,4′-methylenedioxyphenyl)-5-cyano-6-ethylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione (**5h**), and 2,2-dimethyl-5-cyano-6-ethoxycarbonylmethylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione (**5i**), respectively.

Experimental Section

3-Methylthio-3-mercapto-2-cyanothioacrylamide (3a).—Compound 2 was prepared by our method.[11] To the mixture of 2 (17 g, 0.08 mol), sodium hydroxide (6.4 g, 0.16 mol) in water (50 ml), and methanol (50 ml) was added dropwise dimethyl sulfate (7.3 ml, 0.08 mol) under cooling (ice water) and stirring. The reaction mixture was allowed to stand in an icebox for 3 hr. A small amount of solid product was filtered off. It was considered to be 3,3-dimethylthio-2-cyanothioacrylamide by comparison of its ir spectrum with that of the authentic specimen.[11] The yellow filtrate was mixed with 500 ml of water. To the above solution was added 30 ml of concentrated hydrochloric acid. The crude material was filtered, washed with diluted hydrochloric acid, dried in vacuum desiccator for 20 hr, and recrystallized from methanol as yellow needles: yield 15 g, 98%; mp 140–141°; ir (KBr) 3280 (s, NH_3^+), 2200 (vs, conjugated CN), 1593 cm^{-1} (vs, conjugated C=C); nmr (DMSO-d_6) δ 5.00 (br, 3, NH_3^+), 2.48 (s, 3, CH_3); uv $\lambda_{max}^{99\% EtOH}$ 246, 286, 341 mμ (log ϵ 3.60, 3.72, 4.13). *Anal.* Calcd for $C_5H_6N_2S_3$: C, 31.57; H, 3.15; N, 14.72; S, 50.56; mol wt, 190.23. Found: C, 31.68; H, 3.18; N, 14.66; S, 50.60; mol wt, 186 (vapor pressure osmometer, in acetone).

3-Ethylthio-3-mercapto-2-cyanothioacrylamide (3b).—The ethylation of 2 was worked up with diethyl sulfate as mentioned in preparation of **3a**. The resulting yellow material was recrystallized from methanol as yellow needles: yield 94%; mp 149–

(1) M. Yokoyama, *J. Org. Chem.*, **35**, 283 (1970).
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(3) J. E. Jansen and R. A. Mathes, *J. Amer. Chem. Soc.*, **77**, 2866 (1955).
(4) M. Kahan, *Chem. Ber.*, **30**, 1318 (1897).
(5) T. L. Gresham, J. E. Jansen, and F. W. Shaver, *J. Amer. Chem. Soc.*, **70**, 1001 (1948).
(6) R. A. Mathes and F. D. Stewart, U. S. Patent 2,514,004 (1950).
(7) T. Takeshima, T. Hayashi, M. Muraoka, and T. Matsuoka, *J. Org. Chem.*, **32**, 980 (1967).
(8) T. Takeshima, T. Imamoto, M. Yokoyama, K. Yamamoto, and M. Akano, *ibid.*, **33**, 2877 (1968).
(9) T. Takeshima, M. Yokoyama, T. Imamoto, M. Akano, and H. Asaba, *ibid.*, **34**, 730 (1969).
(10) M. Muraoka, M. Yokoyama, K. Yamamoto, and T. Takeshima, *Bull. Chem. Soc. Jap.*, **43**, 2134 (1970).
(11) T. Takeshima, M. Yokoyama, N. Fukada, and M. Akano, *J. Org. Chem.*, **35**, 2438 (1970).

TABLE I

APPEARANCE, MELTING POINTS, AND YIELDS OF COMPOUNDS 5

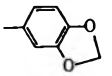
Compd	R	R_1	R_2	Appearance	Mp, °C (cor)	Yield, %
5a	CH_3	$(CH_2)_5$		Yellow plates	219–220 dec	86
5b	CH_3	CH_3	CH_3	Yellow plates	194–195	87
5c	CH_3	H	CH_3	Yellow prisms	174–175	91
5d	CH_3	H	C_6H_5	Yellow prisms	202–203	90
5e	CH_3	H		Yellow plates	184–185 dec	75
5f	C_2H_5	$(CH_2)_4$		Yellow plates	154–155	74
5g	C_2H_5	CH_3	C_2H_5	Yellow plates	161–162	58
5h	C_2H_5	H		Yellow prisms	201–202	89
5i	CH_2CO_2Et	CH_3	CH_3	Yellow prisms	185–186	54

TABLE II

ANALYSES OF COMPOUNDS 5

		Calcd, %				Found, %			
Compd	Formula	C	H	N	S	C	H	N	S
5a	$C_{11}H_{14}N_2S_3$	48.87	5.18	10.36	35.58	48.95	4.99	10.51	35.38
5b	$C_8H_{10}N_2S_3$	41.73	4.34	12.16	41.77	41.93	4.30	12.14	41.55
5c	$C_7H_8N_2S_3$	38.88	3.70	12.95	44.48	38.95	3.68	12.93	44.53
5d	$C_{12}H_{10}N_2S_3$	51.79	3.59	10.06	34.56	51.96	3.39	10.08	34.19
5e	$C_{10}H_8N_2S_3O$	44.73	2.98	10.44	35.85	44.85	3.01	10.64	35.88
5f	$C_{11}H_{14}N_2S_3$	48.87	5.18	10.36	35.58	48.69	5.16	10.50	35.63
5g	$C_{10}H_{14}N_2S_3$	46.47	5.42	10.85	37.25	46.58	5.63	10.93	37.13
5h	$C_{14}H_{12}N_2S_3O_2$	49.97	3.57	8.33	28.61	50.03	3.70	8.50	28.60
5i	$C_{11}H_{14}N_2S_3O_2$	43.68	4.66	9.25	31.80	43.56	4.58	9.40	31.53

TABLE III

MASS SPECTRA OF COMPOUNDS 5[a]

m/e (rel intensity, %)				
5a	5b	5c	5d	5e
270 (100, M^+)	230 (76, M^+)	216 (56, M^+)	278 (67, M^+)	268 (55, M^+)
255 (52, $-CH_3$)	215 (48, $-CH_3$)	201 (30, $-CH_3$)	263 (33, $-CH_3$)	253 (13 $-CH_3$)
237 (15, $-HS$)	197 (19, $-HS$)	187 (17)	245 (8, $-HS$)	235 (5, $-HS$)
223 (48, $-SCH_3$)	183 (43, $-SCH_3$)	183 (10, $-HS$)	231 (19, $-SCH_3$)	221 (42, $-SCH_3$)
190 (39, $-SCH_3 - HS$)	174 (19)	169 (21, $-SCH_3$)	199 (21)	189 (5)
174 (30)	126 (100)	140 (17)	172 (8)	138 (12)
126 (85)		126 (100)	126 (100)	126 (100)

[a] Mass spectra were measured with a Nihon Densi JMS-01 mass spectrometer. Ionizing energy was maintained at 75 eV and the total ionizing current of 200 μA.

TABLE IV

ULTRAVIOLET DATA OF COMPOUNDS 5[a]

Compd	$\lambda_{max}^{99\% EtOH}$, m$\mu$ (log ϵ)
5a	255 (3.58), 288 (3.69), 374 (4.11)
5b	263 (3.10), 287 (3.44), 373 (3.99)
5c	263 (3.39), 290 (3.62), 372 (4.21)
5d	263 (3.27), 298 (3.60), 380 (4.12)
5e	264 (3.53), 300 (3.62), 381 (4.12)
5f	255 (3.64), 291 (3.74), 372 (4.15)
5g	255 (3.50), 289 (3.61), 372 (4.05)
5h	264 (3.74), 295 (3.91), 382 (4.25)

[a] The absorbance measurements were made with a Hitachi EPS-3T type spectrophotometer.

150°; ir (KBr) 3280 (s, NH_3^+), 2200 (vs, conjugated CN), 1605 cm^{-1} (vs, conjugated C=C); nmr (DMSO-d_6) δ 4.30 (br, 3, NH_3^+, 3.10 (q, 2, CH_2, J = 6 Hz), 1.18 (t, 3, CH_3, J = 6 Hz); uv $\lambda_{max}^{99\% EtOH}$ 241, 287, 344 mμ (log ϵ 3.61, 3.39, 4.25) *Anal.* Calcd for $C_6H_8N_2S_3$: C, 35.28; H, 3.92; N, 13.71; S, 47.09; mol wt, 204.24. Found: C, 35.22; H, 3.89; N, 13.88; S, 46.98; mol wt, 218 (vapor pressure osmometer, in acetone).

3-Ethoxycarbonylmethylthio-3-mercapto-2-cyanothioacrylamide (3c).—The ethoxycarbonyl methylation was worked up with ethyl bromoacetate as mentioned in the preparation of **3a**. The crude material was recrystallized from acetic acid and washed with ethanol to give orange needles: yield 24%; mp 129–130°; ir (KBr) 3260 (s, NH_3^+), 2200 (s, conjugated CN), 1720 (vs, CO), 1605 cm^{-1} (vs, conjugated C=C). *Anal.* Calcd for $C_8H_{10}N_2S_2O_2$: C, 36.62; H, 3.84; N, 10.67; S, 36.66; mol wt, 232.34. Found: C, 36.36; H, 3.73; N, 10.69; S, 36.61; mol wt, 258 (vapor pressure osmometer, in acetone).

5-Cyano-6-methylthio-2,3-dihydro-4*H*-1,3-thiazine-4-thione-2-spirocyclohexane (5a).—A solution of **3a** (2.5 g, 0.013 mol), cyclohexanone (5 g, 0.05 mol), and a 2% aqueous solution of sulfuric acid (10 ml) in 30 ml of ethanol was refluxed for 5 min. The yellow material was collected and recrystallized from pyridine–water, yield 3 g.

Compounds **5b–i** were prepared in the same method as mentioned in the preparation of **5a**. The ir and nmr spectral data of compounds 5 were summarized in Tables V and VI.

TABLE V

INFRARED DATA (KBr) OF COMPOUNDS 5

	Tentative assignment, frequency, cm^{-1}			
Compd	ν_{NH}	$\nu_{conjd\ CN}$	$\nu_{conjd\ C=N}$	
5a	3120 (s)	2210 (s)	1520 (vs)	
5b	3120 (s)	2210 (s)	1520 (vs)	
5c	3120 (s)	2200 (s)	1530 (vs)	
5d	3180 (s)	2210 (s)	1520 (vs)	
5e	3120 (s)	2200 (s)	1520 (vs)	
5f	3180 (s)	2220 (s)	1520 (vs)	
5g	3120 (s)	2210 (s)	1530 (vs)	
5h	3120 (s)	2210 (s)		1605 (w, benzene)
5i	3130 (s)	2220 (s)	1520 (vs)	1720 (vs, CO)

TABLE VI

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR COMPOUNDS 5[a]

Compd	δ values in DMSO-d_6
5a	10.42 (s, 1, NH), 2.68 (s, 3, SCH_3), 2.04 (br, 4, C(2′, 6′)H_2), 1.62 (br, 6, C(3′, 4′, 5′)H_2)
5b	10.48 (s, 1, NH), 2.68 (s, 3, SCH_3), 1.70 (s, 6, $2CH_3$)
5c	10.47 (br, 1, NH), 5.10 (m, 1, CH), 2.68 (s, 3, SCH_3), 1.60 (d, 3, CH_3, J = 5 Hz)
5e	10.86 (br, 1, NH), 7.75 (s, 1, CH), 6.48 (s, 3, C_4H_3O), 2.66 (s, 3, SCH_3)
5f	10.68 (s, 1, NH), 3.18 (q, 2, CH_2CH_3, J = 6 Hz), 2.12 (br, 4, C(3′, 4′)H_2), 1.76 (br, 4, C(2′, 5′)H_2), 1.32 (t, 3, CH_2CH_3, J = 6 Hz)
5g	10.52 (s, 1, NH), 3.20 (q, 2, SCH_2CH_3, J = 6 Hz), 1.98 (q, 2, CH_2CH_3, J = 6 Hz), 1.62 (s, 3, CH_3), 1.32 (t, 3, SCH_2CH_3, J = 6 Hz), 0.92 (t, 3, CH_2CH_3, J = 6 Hz)
5h	10.83 (br, 1, NH), 6.96 (d, 3, C_6H_3), 6.22 (d, 1, CH, J = 4 Hz), 6.06 (s, 2, CH_2), 3.14 (q, 2, SCH_2CH_3, J = 6 Hz), 1.26 (t, 3, SCH_2CH_3, J = 6 Hz)
5i	10.70 (s, 1, NH), 4.20 (s, 2, CH_2), 4.10 (q, 2, CH_2CH_3, J = 6 Hz), 1.65 (s, 6, $2CH_3$), 1.20 (t, 3, CH_3CH_3, J = 6 Hz)

[a] Recorded on a JNM-C-60 high-resolution nmr spectometer operating at 60 MHz using tetramethylsilane as an internal standard.

Registry No.—**3a**, 29082-78-8; **3b**, 29082-79-9; **3c**, 29082-80-2; **5a**, 29082-81-3; **5b**, 29082-82-4; **5c**, 29082-83-5; **5d**, 29082-84-6; **5e**, 29082-85-7; **5f**, 29082-86-8; **5g**, 29082-87-9; **5h**, 39082-88-0; **5i**, 29082-89-1.

Acknowledgment.—The author wishes to express his thanks to Professor Dr. Tatsuo Takeshima and Dr. Hiroshi Midorikawa for their helpful discussion and encouragement throughout the course of this work.

The Conformation of 1,4-Dihydro-1-naphthoic Acid from the Nuclear Magnetic Resonance Spectrum

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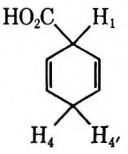
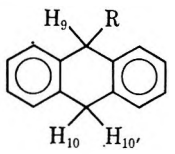
We recently discussed the long-range splitting between the 1 and 4 protons in 1,4-dihydrobenzoic acid (**1**).[1] This extremely large value of $J_{1,4}$ (8–9 Hz)[2] is somewhat surprising when compared with the negligibly small $J_{9,10}$ values of 9,10-dihydroanthracenes.[3,4] To explain the difference between $J_{1,4}$ in **1** and $J_{9,10}$ in **2**, we considered two possibilities: (1) **1** is flat and **2** is not, and the angular dependence of $J_{1,4}$ is such that the 1 and 4 protons couple when the dihydrobenzene ring is flat, but do not couple when the ring is in the boat conformation;[5] (2) the spin–spin interaction between the 1 and 4 protons is conveyed



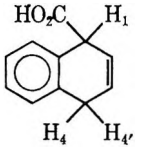
1



2

by an olefin, but not by an aromatic, π system.[6] To decide which explanation is correct, it is necessary to know whether 1,4-dihydrobenzenes and 9,10-dihydroanthracenes are flat. It is known that dihydroanthracenes are not flat (by the nmr chemical nonequivalence of the two 10 protons),[3,4] but, unfortunately, it is not known whether the dihydrobenzene system is relatively flat.[7,8]

It was thought that a good test molecule to help resolve these difficulties would be 1,4-dihydro-1-naphthoic acid (**3**). This molecule possesses both an aromatic ring, whose ring currents would cause the two 4 protons to be chemically nonequivalent and would thus demonstrate the molecule to be nonplanar if it indeed were so, and also an olefin to transmit the spin–spin interaction if explanation 2 were operative. Therefore, **3** was synthesized by the Birch reduction[9] of 1-naphthoic acid and an nmr study of **3** was undertaken.



3

The 60-MHz nmr spectrum of **3** showed five regions of signals centered at δ 11.5, 7.3, 6.2, 4.6, and 3.6 that integrated in the respective ratio of 1, 4, 2, 1, and 2. Unlike the case of 1,4-dihydrobenzoic acid,[1] the spectral pattern of **3** was so complex that a complete 60-MHz analysis was impossible. Therefore, the 100-MHz spectrum was taken and studied. Decoupling experiments and use of the LAOCOON III nmr computer program[10] led to a set of parameters for the protons 1, 2, 3, 4, and 4′. These parameters are given in Table I.

(1) J. L. Marshall, K. C. Erickson, and T. K. Folsom, *J. Org. Chem.*, **35**, 2038 (1970).

(2) For other examples of large homoallylic couplings in 1,4-dihydrobenzenes, see E. W. Garbisch, Jr., and M. G. Griffith, *J. Amer. Chem. Soc.*, **90**, 3590 (1968); D. J. Atkinson and M. J. Perkins, *Tetrahedron Lett.*, 2335 (1969); L. J. Durham, J. Studebaker, and M. J. Perkins, *Chem. Commun.*, 456 (1965).

(3) D. Nicholls and M. Szwarc, *J. Amer. Chem. Soc.*, **88**, 5757 (1966); R. G. Harvey, L. Arzadon, J. Grant, and K. Urberg, *ibid.*, **91**, 4535 (1969).

(4) A. W. Brinkman, M. Gordon, R. G. Harvey, P. W. Rabideau, J. B. Stothers, and A. L. Ternay, Jr., *ibid.*, **92**, 5912 (1970).

(5) Theory predicts that the size of the homoallylic coupling constant varies as $\cos^2\phi \cdot \cos^2\phi'$ with the two angles ϕ and ϕ' each being the dihedral angle between each C–H bond and the intervening p orbitals of the π system: M. Karplus, *J. Chem. Phys.*, **33**, 1842 (1960); M. Barfield, *ibid.*, **48**, 4463 (1968).

(6) There is a theoretical basis for this explanation. If one assumes that the proton–proton coupling is dominated by a (nuclear-spin)–(electron-spin)–(electron-spin)–(nuclear-spin) coupling mechanism, then coupling *via* olefin bonds can be calculated to rather large and *via* aromatic bonds to be rather small: H. M. McConnell, *ibid.*, **30**, 126 (1959).

(7) See ref 2. See also B. A. Shoulders, R. M. Gipson, R. J. Jandacek, S. H. Simonsen, and W. Shive, *J. Amer. Chem. Soc.*, **90**, 2992 (1968); F. H. Herbstein, *J. Chem. Soc.*, 2292 (1959).

(8) The conformation of 1,4-dihydrobenzene itself is known to be very slightly puckered: H. Oberhammer and S. H. Bauer, *J. Amer. Chem. Soc.*, **91**, 10 (1969).

(9) M. E. Kuehne and B. F. Lambert, *Org. Syn.*, **43**, 22 (1963). For the synthesis of **3**, see the Experimental Section.

(10) A. A. Bothner-By and S. M. Castellano, "Computer Programs for Chemistry," Vol. 1, D. F. DeTar, Ed., W. A. Benjamin, New York, N. Y., 1968, p 10.

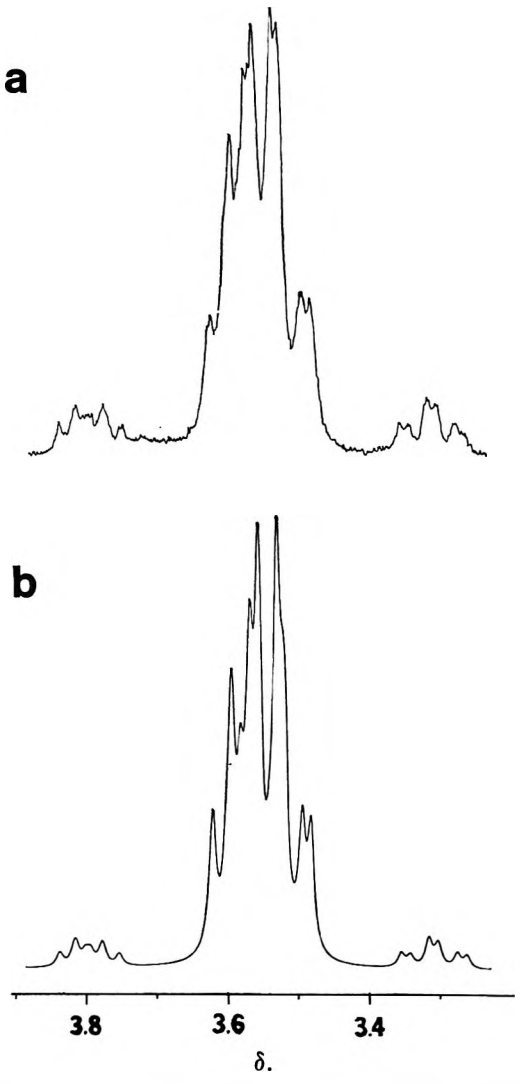


Figure 1.—(a) Observed and (b) computer-simulated spectral regions for methylene protons (H_4, $H_{4'}$) of 1,4-dihydro-1-naphthoic acid.

TABLE I
NMR PARAMETERS FOR 1,4-DIHYDRO-1-NAPHTHOIC ACID (3)[a]

Proton	Chemical shift, δ	$J_{A,B}$ A	B	Hz
1	4.55			
2	6.07			
3	6.25	1	2	4.59
4	3.47	1	3	−1.22
4′	3.63	1	4	3.93
		1	4′	3.93
		2	3	9.62
		2	4	−1.24
		2	4′	−2.97
		3	4	4.60
		3	4′	2.44
		4	4′	−21.92

[a] These final values were obtained by using the iterative subroutine of the LAOCOON III nmr computer program[10] to obtain the best fit of the data. The rms error was 0.07 Hz.

Figures 1, 2, and 3 show the observed and computer-simulated patterns of the methylene region (H_4, $H_{4'}$), the methine region (H_1), and the olefin region (H_2, H_3), respectively.

Two notable differences exist between the spectral patterns for 1,4-dihydrobenzoic acid[1] and for 1,4-dihydro-1-naphthoic acid. First, the two methylene protons (H_4 and $H_{4'}$) in **3** now have different chemical shifts. This can be explained by the nonplanarity of the dihydro ring which places the methylene protons in different chemical environments (pseudoaxial and pseudoequatorial).

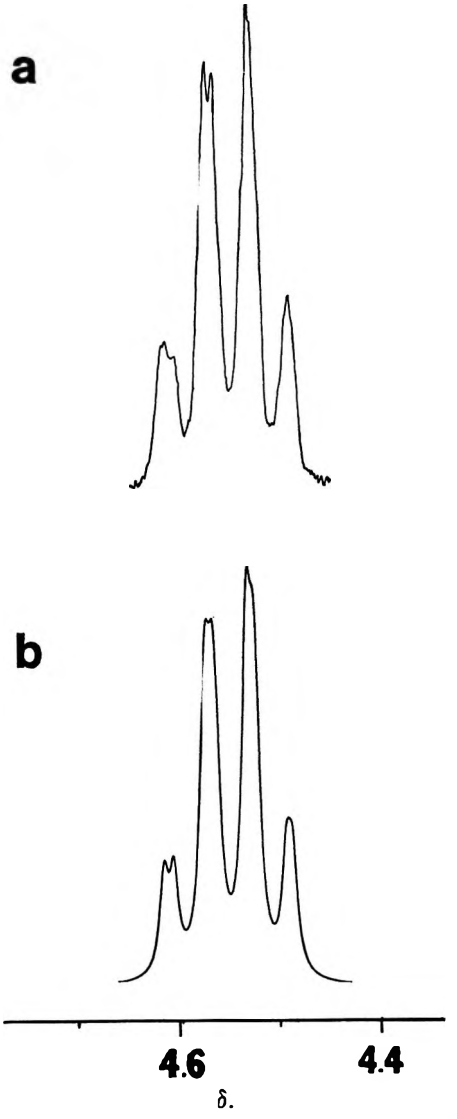


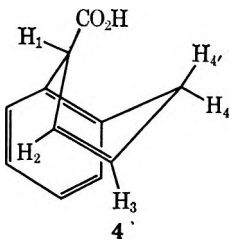
Figure 2.—(a) Observed and (b) computer-simulated spectral regions for the methine proton (H_1) of 1,4-dihydro-1-naphthoic acid.

Second, the olefin protons in **3** now couple significantly with the methine (H_1) and the methylene (H_4, $H_{4'}$) protons. This again suggests nonplanarity of the ring in **3**, because calculations[11] indicate that this coupling decreases as the ring becomes more planar. 1,4-Dihydrobenzoic acid, which has negligible olefin–methylene and olefin–methine coupling,[1] is thus indicated to be more nearly flat.

A clue to which methylene proton is pseudoequatorial and which is pseudoaxial is given by the vicinal coupling constants $J_{3,4}$ and $J_{3,4'}$. The dihedral angle involving H_3 and the pseudoaxial proton is more nearly 90° than that involving H_3 and the pseudoequatorial proton (see **4**). Since J_{vic} decreases as the dihedral angle approaches 90°[11-13] and since $J_{3,4}$ (4.60 Hz) is greater

(11) K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.*, **83**, 4623 (1961); M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(12) S. Sternhell, *Quart. Rev., Chem. Soc.*, **23**, 236 (1969).
(13) A. A. Bothner-By, S. Castellano, S. J. Ebersole, and H. Gunther, *J. Amer. Chem. Soc.*, **88**, 2466 (1966).

than $J_{3,4'}$ (2.44 Hz), then $J_{3,4}$ must involve the pseudoequatorial proton. Thus, H_4 must be pseduoequatorial and $H_{4'}$ must be pseudoaxial, as indicated in **4**.[14]



4

The J_{vic} values can also place the position of the carboxylate group. $J_{1,2}$ (4.59 Hz) is virtually equal to $J_{3,4}$ (4.60 Hz). Since H_4 is pseudoequatorial, H_1 must also be pseudoequatorial.[15] Structure **4** thus represents the correct conformation of **3** with the carboxylate group in the pseudoaxial position.[16] Apparently the group prefers this position because of interactions with the aromatic ortho proton when in the pseudoequatorial position.

A check on the above assignments can be made by means of the allylic coupling constants. Calculations[12,17] indicate that, when a C–H bond (of an sp^3 carbon atom) is parallel to the adjacent p orbital of a π bond, the allylic coupling constant is maximum (around 3.0 Hz), and, when perpendicular, more nearly zero. Therefore, from **4** one would predict $J_{2,4'}$ to be about 3 Hz and $J_{1,3}$ and $J_{2,4}$ to be smaller and approximately equal to one another. Precisely as predicted, $J_{2,4'}$ = 2.97 Hz, $J_{1,3}$ = 1.22 Hz, and $J_{2,4}$ = 1.24 Hz. Thus, from an analysis of the vicinal and allylic coupling constants, **4** seems to be the correct conformation of 1,4-dihydro-1-naphthoic acid.

The homoallylic coupling $J_{1,4}$ and $J_{1,4'}$ is significant in **3** as in the case of **1**. In view of the present indications that **1** is more nearly planar than **3**,[18] this homoallylic coupling apparently does not depend upon the planarity of the ring (although its magnitude might). Thus, from the first paragraph above it follows that the homoallylic spin–spin interaction is transmitted through the olefin bond but cannot be transmitted significantly through an aromatic bond.

It would be of interest to determine the J_{cis}/J_{trans} ratio in **3** to see if this ratio reflects the degree of puckering in the dihydro ring.[1] Unfortunately, all of the parameters of Table I are definite *except* $J_{1,4}$ and $J_{1,4'}$; small changes in all parameters (~0.1 Hz) except $J_{1,4}$ and $J_{1,4'}$ caused significant changes in the appearance of the simulated[10] nmr spectrum. To obtain this ratio directly, we are currently investigating the nmr spectra of the deuterated analogs of 1,4-dihydro-1-naphthoic acid.

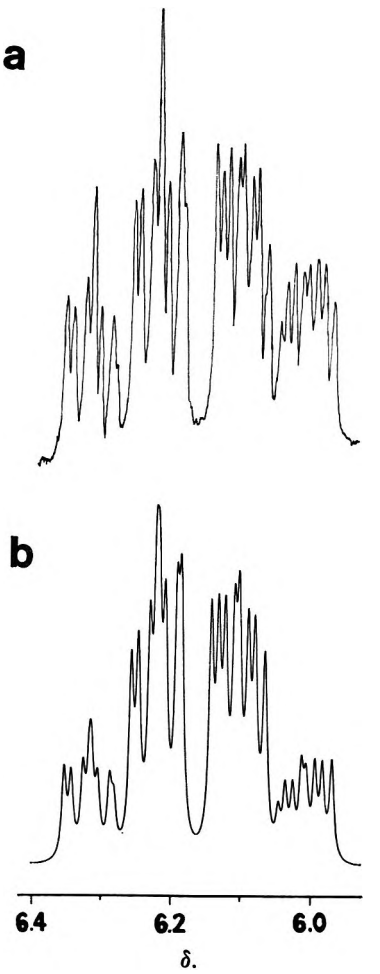


Figure 3.—(a) Observed and (b) computer-simulated spectral regions for olefin protons (H_2, H_3) of 1,4-dihydro-1-naphthoic acid.

Experimental Section

Melting points were determined by a Thomas-Hoover melting point apparatus. Nuclear magnetic resonance spectra were recorded on a Jeolco MH-60 spectrometer and a Jeolco PS-100 spectrometer, using tetramethylsilane as the internal standard and deuteriochloroform as the solvent.

1,4-Dihydro-1-naphthoic Acid (3).—Into a 1000-ml three-necked flask equipped with a mechanical stirrer and a Dry Ice condenser was distilled 300 ml of ammonia under an argon atmosphere. To the stirring contents was added 5.0 g of 1-naphthoic acid (Aldrich Chemical Co.), 50 ml of dry ethanol (distilled from calcium), and then 2.2 g of sodium metal in small pieces. After 30 min of stirring, 5.4 g of ammonium chloride was added cautiously. After 1 hr of stirring, the ammonia was evaporated and 150 ml of water was added. Sufficient hydrochloric acid (6 *N*) was added to bring the pH to 8. The solution was filtered, made acidic with 6 *N* hydrochloric acid, and extracted with four 60-ml portions of ether. The combined ethereal extracts were dried (anhydrous magnesium sulfate) and concentrated under reduced pressure to give a brown solid. Recrystallization from 60–90° petroleum ether gave 3.10 g of **3** (61%), mp 87–89° (lit.[19] mp 86°). The mother liquor was concentrated to give 1.22 g of a brown solid, mp 69–76°, whose nmr analysis indicated it to be a 1:1 ratio of **3** and the isomeric 3,4-dihydro-1-naphthoic acid. Recrystallization of the 87–89° material gave a pure nmr sample, mp 88.5–90.5°.

(14) These values of J_{vic} are consistent with previous examples: $J_{2,3}$ in cyclohexene (a flexible system where $J_{2,3} = J_{2,3'}$) is 3.1 Hz [C. V. Smith and H. Kriloff, *ibid.*, **85**, 2016 (1963)].

(15) The electronegative effect of the carboxylate substituent upon $J_{1,2}$ would probably be negligible and in any case should decrease the value of $J_{1,2}$ (see ref 11). Thus, in the absence of the electronegative effect, the value of $J_{1,2}$ represents a minimal value and $J_{1,3}$ certainly corresponds with $J_{1,4}$.

(16) The 9 substituent in 9-alkyl-9,10-dihydroanthracenes is also pseudoaxial [see ref 4].

(17) M. Barfield, *J. Chem. Phys.*, **41**, 3825 (1964).

(18) As a referee pointed out, theory[5] predicts that $J_{1,4} \simeq J_{1,4'}$ is only consistent with a planar molecule for **3**. Previous work [D. W. Cameron, D. G. I. Kingston, N. Sheppard, and L. Todd, *J. Chem. Soc.*, 98 (1964); J. T. Pinhey and S. Sternhell, *Tetrahedron Lett.*, 275 (1963); H. H. Appel, R. P. M. Bond, and K. H. Overton, *Tetrahedron*, **19**, 635 (1963)] indicates that (pseudoequatorial)–(pseudoequatorial) coupling should be very small. However, the conformation of the rings described in these references was not always independently definable, and in those examples involving fixed geometries at least some probably involve half chairs. Hence, the utility of the homoallylic coupling as a tool for conformational analysis has not been established.

(19) K. von Auwers and K. Moller, *J. Prakt. Chem.*, **109**, 144 (1925).

Registry No.—**3**, 5111-73-9.

Acknowledgment.—Acknowledgment is made to the Research Corporation (Frederick Gardner Cottrell Grant-in-Aid), to the Robert A. Welch Foundation (Grant No. B-325), and to North Texas State University for a Faculty Research Grant for support of this work.

The Dipole Moments and Conformations of 1,2-Diimines

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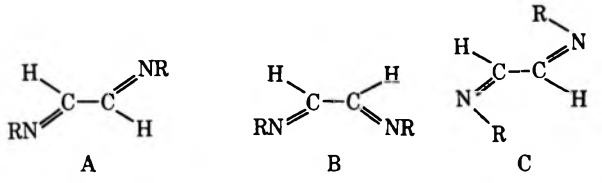
Studies on the reaction of glyoxal with aliphatic[1] and aromatic[2] amines have led, in certain cases, to the isolation of N,N′-substituted 1,2-diimines. Their configuration was shown to be *E* (anti) at both C=N double bonds by analysis of their nmr spectra, the course of protonization, and by analogy with other aldimines,[3-5] whereas the conformation of the central C—C bond was only tentatively attributed to be s-trans A rather than s-cis B. A more detailed study of this conformation is the aim of the present paper.



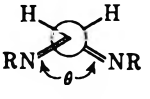
From *a priori* considerations, it follows that both planar forms are stabilized by mesomerism, the s-trans form A being more favored than s-cis B. However, the double bond character of the central bond cannot be very accurately expressed since the corresponding mesomeric formula is destabilized by charge separation and by a sextet on the nitrogen atoms. Hence, the planarity can easily be distorted by nonbonded interactions. For the same reasons the conformation of 1,2 diketones is nonplanar.[6]

Our experimental method of choice was dipole moment measurement in solution. Admittedly, this approach is of limited accuracy; however, because the results are extrapolated to zero concentration, it has the advantage that a practically isolated molecule is studied in a nonpolar medium. The accuracy can be improved by measuring several substituted derivatives and comparing experimental and computed moments graphically.[7]

The experimentally measured dipole moments are given in Table I and can be considered internally consistent, especially the values for compounds **1**, **2**, and **5**, which should be equal according to the simple method of vector addition, and, in fact, are reasonably close to each other. In general, the measurements are not very precise because of association in solution, thus making extrapolation difficult. However, the situation is much improved for the measurements taken on compounds **5** and **6**. Therefore, our discussion is mainly based on these compounds for which the standard accuracy was attained, limited ultimately by the correction for atomic polarization (compare columns 7 and 8 in Table I). When the compounds are measured in two solvents, the differences are significant.

Without any computation, one can conclude from the nonzero experimental moments that a strictly planar conformation *E*-s-trans-*E*, A, is not possible, neither is the *Z*-s-trans-*Z* one, C. When the *E* configuration is taken for granted, the experimental results can be interpreted either as a mixture of both forms A and B or as a nonplanar conformation of the C_2 symmetry. On the basis of dipole moment data, one cannot discern between these two possibilities. However, on the basis of the results on 1,2 diketones[6] and glyoximes[8] we prefer the latter.

In order to get a more quantitative picture it is necessary to compute theoretical moments for individual compounds in conformation B. Starting from trigonal valence angles and the C=N bond moment of 1.8 D[9] we get the same value, 3.12 D, for compounds **1**, **2**, **3**, **5**, and **6**, indicating the dihedral angle N–C–C–N in the real conformation to be between 90 and 140°.[10] The



$\theta = 90$–$140°$

computation is rather sensitive to the valence angles used. A smaller C–N–C angle, *e.g.*, 117°, as found in *N*-methylmethyleneimine,[11] or a larger C–C–N angle would lead to a greater moment for the methyl deriva-

(1) J. M. Kliegman and R. K. Barnes, *Tetrahedron*, **26**, 2555 (1970); *Tetrahedron Lett.*, 1953 (1969).
(2) J. M. Kliegman and R. K. Barnes, *J. Org. Chem.*, **35**, 3140 (1970).
(3) V. de Gaouck and R. J. W. Le Févre, *J. Chem. Soc.*, 741 (1938).
(4) G. J. Karabatsos and S. S. Lande, *Tetrahedron*, **24**, 3907 (1968).
(5) J. Hine and C. Y. Yeh, *J. Amer. Chem. Soc.*, **89**, 2269 (1967).
(6) P. H. Cureton, C. G. Le Févre, and R. J. W. Le Févre, *J. Chem. Soc.*, 4447 (1961).
(7) O. Exner and V. Jehlička, *Collect. Czech. Chem. Commun.*, **30**, 639 (1965).
(8) A nonplanar conformation with a dihedral angle N–C–C–N *ca.* 120–140° has been also preferred for glyoximes. A more exact determination is, in this case, prevented by possible distortion of the O–N bonds: C. Pigenet, J. Armand, and H. Lumbroso, *Bull. Soc. Chim. Fr.*, 2124 (1970).
(9) O. Exner, *Collect. Czech. Chem. Commun.*, **30**, 652 (1965).
(10) Compounds **4** and **7** are complicated by additional rotations such as those shown in i and ii. Thus our data does not allow us to make any comparison of computed and measured values.

(11) K. V. L. N. Sastry and R. F. Curl, *J. Chem. Phys.*, **41**, 77 (1964).

TABLE I

POLARIZATION DATA OF 1,2-DIIMINES RN=CHCH=NR AT 25°

No.	Registry no.	R	Mp, °C	Solvent[a]	$_{\infty}P_2$,[b] cm³	R_D[c] (calcd), cm³	μ (5%),[d] D	μ (15%),[d] D
1	28387-17-9	C_4H_9	1.4548[e]	B	80.8	53.7	1.09	0.96
2	28227-40-9	i-C_4H_9	1.4518[e]	B	85.3	53.7	1.28	1.27
3	28227-38-5	c-C_6H_{11}	145–147	B	123.0	67.8	1.59	1.48
4	24978-40-3	2-$CH_3C_6H_4$	122–124	B	106.6	77.4	1.11	1.93
5	24978-41-4	4-$CH_3C_6H_4$	164–165	B	113.9	77.4	1.26	1.10
				D	160.2	77.4	1.96	1.87
6	24978-44-7	4-ClC_6H_4	107–110	B	183.0	78.0	2.22	2.14
				D	241.3	78.0	2.79	2.72
7	24978-42-5	4-$CH_3OC_6H_4$	153–154	B	196.7	81.9	2.32	2.24

[a] B, benzene; D, dioxane. [b] Overall polarization. [c] Molar refraction. [d] Correction for the atomic polarization, 5 or 15% of the R_D value, respectively. [e] $n^{25}D$.

tive **5** than for the 4-chloro derivative **6**. Quite on the contrary, the experimental value is significantly smaller showing that either the C–N–C angle is larger or the C–C–N angle smaller, or more probably that the conformation of both compounds **5** and **6** is somewhat different. The situation is pictured by a graphical representation used in our previous papers[7,9] (Figure 1). Computed moments for various dihedral angles are shown by straight lines, the full line corresponding to angles C–N–C = C–C–N = 120°, the broken one to a change of one of them by 5°. From the experimental point it can be concluded that the conformations of both compounds **5** and **6** may differ.[12] A more exact determination of dihedral angles from our data is not possible.

It should be stressed once more that all the results were obtained with a precondition of the *E* configuration on the C=N double bond. For the *Z* configuration the theoretical dipole moments can also be computed. The results in that case are still dependent on the value for the C—N bond, whereas the mesomeric moment can be neglected since the benzene rings are not coplanar with the C=N bonds.[13] It is, however, not possible to distinguish between all various possibilities from the values of dipole moments alone.

We conclude that nonplanar stable conformations are typical for the atom grouping X=CC=X; evidently the mesomerism is not strong enough to overcome the bond and atom repulsion. The conformation is not very rigid and differs somewhat in vapor and in the crystalline state, in various solvents, and at different temperatures.[6] This behavior is contrasted by that of 1,3-butadiene which has two energetical minima in its two planar conformations, differing by 2.3 kcal mol^{-1} and separated by a barrier of 2.6 kcal mol^{-1} (*cf.* ref 14). For 1,2 diketones, theoretical calculations which furnished the energy difference between the two planar forms, however, did not reveal the existence of an energetical minimum.[15] Similarly, in the case of 1,2-diimines no more quantitative discussion is possible at the present time.[8]

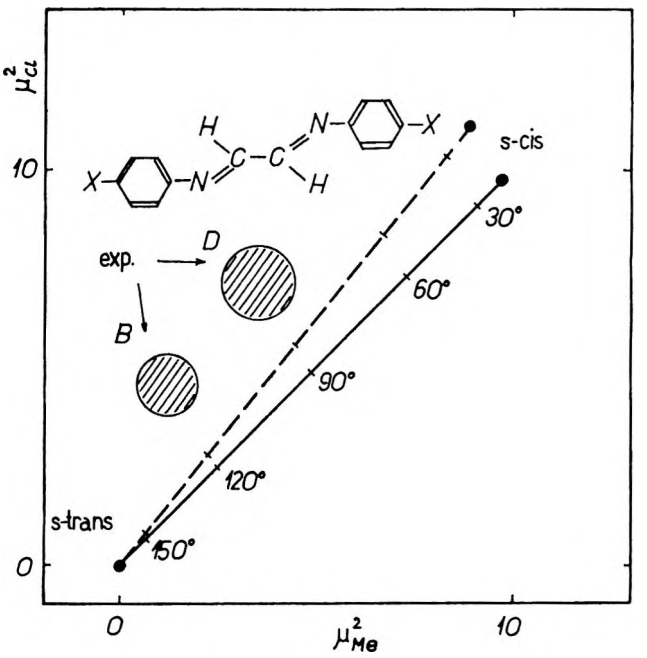


Figure 1.—Comparison of computed (straight lines) and experimental dipole moments (circles) of compounds **5** and **6** in benzene (B) and dioxane (D) over a range of bond angles.

Experimental Section

The preparation of compounds **1–7** has been previously described.[1,2] Dipole moments were determined by the method of Halverstadt and Kumler.[16] Dielectric constants of benzene or dioxane solutions were measured at 25° using a heterodyne apparatus at a frequency of 1.2 Mcps. Usually five measurements were carried out in the concentration range 5×10^{-3}–5×10^{-2} *M*. The molar refractions were calculated from Vogel's increments[17] and suitable additive corrections (exaltations) applied in order to account for the conjugation, *viz.*, 0.4 cm³ for the conjugation of two C=N bonds and 1.5 cm³ for the conjugation of one C=N bond with a benzene nucleus. The inaccuracy in this procedure does not influence the final values of dipole moments significantly.

Acknowledgment.—The measurement of dielectric constants and densities was carried out by Mrs. M. Kuthanová, Department of Physical Chemistry, Institute of Chemical Technology, Prague, under the supervision of Dr. V. Jehlička. The aid of both is gratefully acknowledged.

(12) A rough estimate of the dihedral angles for compounds **1–3**, and **5** and **6** would be 135–145°, 130–140°, 120–130°, 130–140°, and 90–100°, respectively.

(13) V. I. Minkin, Y. A. Zhdanov, E. A. Medyantzeva, and Y. A. Ostroumov, *Tetrahedron*, **23**, 3651 (1967).

(14) J. G. Aston, G. Szasz, H. W. Woolley, and F. G. Brickwedde, *J. Chem. Phys.*, **14**, 67 (1946).

(15) L. V. Vilkov, N. I. Sadova, and N. A. Tarasenko, *Zh. Strukt. Khim.*, **10**, 403 (1969).

(16) I. F. Halverstadt and W. D. Kumler, *J. Amer. Chem. Soc.*, **64**, 2988 (1942).

(17) A. I. Vogel, *J. Chem. Soc.*, 1842 (1948).

Model Reactions for the Metabolism of Thyroxine. II. Reaction of Thyropropionic Acid with Hydroxyl Radical[1]

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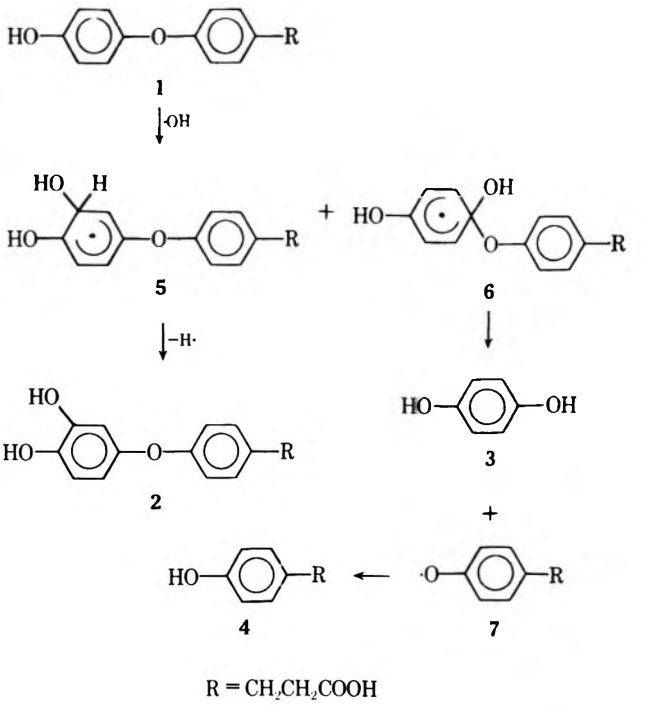
Received December 23, 1970

The rupture of the diphenyl ether linkage in thyronines has been considered to be one of the possible metabolic pathways of thyronines,[2] although Pittman and Chambers[3] reported that in the rat the major excretion products arising from administrated thyroxine still had an intact diphenyl ether structure. It has been shown in the previous papers that the rupture of the diphenyl ether linkage takes place easily by autoxidation of 3′-hydroxythyropropionic acid[4] and by autoxidation of 3′,5′-unsubstituted thyronines and their analogs in the presence of *tert*-butoxide in dimethyl sulfoxide.[5] In the course of studies on the hydroxylation of thyropropionic acid (**1**) for the preparation of 3′-hydroxythyropropionic acid (**2**), we found a direct cleavage of the diphenyl ether linkage of **1**.



thyropropionic acid (**2**) and the rupture of the diphenyl ether linkage giving hydroquinone (**3**) and phloretic acid (**4**) occur simultaneously. While the total yield of

TABLE I

PHOTOLYSIS OF THYROPROPIONIC ACID AND HYDROGEN PEROXIDE[a]

Run	1, mmol	H_2O_2, mmol	Initial pH	Final pH	Decomposed H_2O_2, mmol	Recovered 1, %	Yields of products, %[b] 2	3	4
1	2	50.5	8.8	6.5	2.6	20	33	15	6
2	2	33.6	9.0	7.5	1.9	28	38	11	4
3	2	16.8	9.2	8.5	1.8	31	44	12	1.5
4	2	5.05	9.1	9.1	0.4	51	20	7	0
5	2	0	9.2	9.2		98	0	0	0

[a] See Experimental Section. [b] Yields were based on the amount of 1 consumed.

Omura and Matsuura have reported the hydroxylation of phenols with the hydroxyl radical generated by the photodecomposition of hydrogen peroxide in aqueous media and also in acetonitrile.[6] They have shown that the hydroxylation occurs at the ortho and para positions but not at the meta position and that a methoxy group at the para position with respect to the phenolic hydroxyl is replaced by a hydroxy group in addition to simultaneous ortho hydroxylation.

This method was applied to thyropropionic acid (**1**). A solution of **1** and various amounts of hydrogen peroxide in aqueous sodium hydroxide was irradiated with a low-pressure mercury lamp of Vycor housing under bubbling nitrogen at 0°. The products were analyzed by vpc. The results summarized in Table I showed that hydroxylation at the 3′ position giving 3′-hydroxy-**3** and **4** increased with increasing amount of hydrogen peroxide, the optimum yield of **2** was obtained at limited concentrations of hydrogen peroxide. Photolysis without hydrogen peroxide at 0° led to the recovery of the starting material, but at room temperature a complex mixture was obtained.

The formation of **2**, **3**, and **4** can be rationalized by a scheme similar to that proposed earlier.[6] Of two cyclohexadienyl radicals **5** and **6**, which are formed by the addition of hydroxyl radicals to **1**, **5** loses a hydrogen atom to give **2**, and **6** cleaves to **3** and a phenoxy radical **7** which then abstracts hydrogen to give **4**.

The present reaction provides nonenzymic models for the direct cleavage of the diphenyl ether linkage of thyronines without 3′ hydroxylation in their metabolic pathways and also for the hydroxylation of thyronines to 3′-hydroxythyronines, in addition to the previous model in which the hydroxylation of thyronine at the 3′ position was carried out with the ferrous ion–ascorbic acid–oxygen system.[7]

Experimental Section

General Procedure.—To a solution of 516 mg (2 mmol) of thyropropionic acid[4] in 25 ml of 0.1 *N* sodium hydroxide was added the given amount of 30% hydrogen peroxide, and the

(1) Part I: T. Matsuura, T. Nagamachi, A. Nishinaga, H. Kon, and H. J. Cahnmann, *J. Org. Chem.*, **34**, 2554 (1969). This work was supported by a research grant (AM 07955) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(2) J. E. Rall, J. Robins, and C. G. Lewallen, "The Hormones," G. Pincus, K. V. Thimann, and E. B. Astwood, Ed., Vol V, Academic Press, New York, N. Y., 1964, p 249.

(3) C. S. Pittman and J. B. Chambers, Jr., *Endocrinology*, **84**, 705 (1969).

(4) T. Matsuura, T. Nagamachi, A. Nishinaga, H. Kon, and H. J. Cahnmann, *J. Org. Chem.*, **34**, 2554 (1969).

(5) A. Nishinaga, T. Nagamachi, T. Matsuura, *Chem. Commun.*, 888 (1969).

(6) K. Omura and T. Matsuura, *ibid.*, 127 (1966); *Tetrahedron*, **24**, 3475 (1968); **26**, 255 (1970).

(7) S. Lissitzky and M. Roques, *Bull. Soc. Chim. Biol.*, **39**, 521 (1957).

mixture was diluted with water to a total volume of 100 ml. The solution was internally irradiated with a low-pressure mercury lamp (*ca.* 10 W) of Vycor housing, under bubbling nitrogen, at 0° for 5 hr. An aliquot (10 ml) was subjected to analysis for hydrogen peroxide and the remaining portion was treated with 6 g of sodium bisulfite under ice cooling. The reduced mixture was extracted with ether (total volume, 350 ml). The ethereal layer was washed with a small volume of water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was analyzed by vpc. The products were identified by a comparison with authentic samples.

Analysis.—Hydrogen peroxide was analyzed by iodometry. For vpc analysis the residue from the above ether extract was mixed with 50 mg of diphenyl (internal standard) and then the mixture was treated with an excess of *N,O*-bis(trimethylsilyl)-acetamide in a small volume of absolute benzene. The silylated mixture was analyzed by vpc using a 25% silicone DC 550-on-celite column (1100 × 3 mm).

Registry No.—1, 500-81-2; hydroxyl radical, 3352-57-6.

Electrochemical Preparation of Highly Strained Hydrocarbons. IV. Controlled Potential Electrolysis

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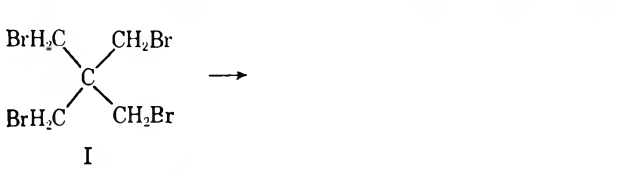
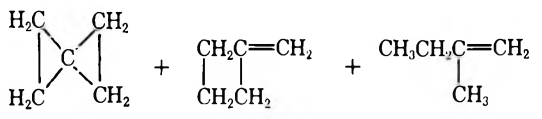
Received November 16, 1970

Previous papers in this series[1-3] reported the use of electrolysis as a tool for the preparation of small-ring compounds such as cyclopropane, cyclobutane, bicyclobutane, and spiropentane from the reduction of appropriate α,ω-dihalides. We would now like to describe an important advantage that this technique has, particularly under controlled potential electrolysis (CPE), over conventional reducing agents in organic synthesis.

The reduction of 1,3-dibromobis(bromomethyl)propane (I) by conventional reducing agents has been described[4-6] as forming a variety of products which included the compounds shown below. Under uncontrolled potential electrolysis, however, compound I was reduced to give spiropentane in high yield.[7]



I



II III IV

The formation of compounds II–IV from I under uncontrolled potential electrolysis or by conventional reducing agents presumably takes place through a common intermediate, namely 1,1-bromomethylcyclopropane (V). Subsequent reduction of this intermediate under the above reaction conditions has not allowed its isolation. Thus, the electrolysis of I under controlled potential was investigated to isolate the presumed intermediate V and to compare the utility of CPE with conventional reduction methods in organic synthesis.

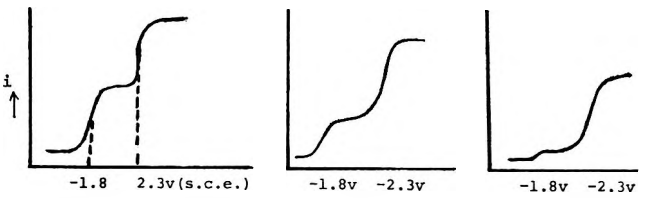
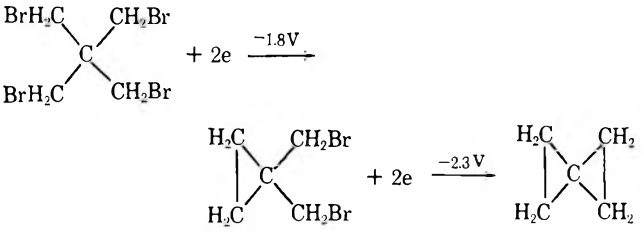


Figure 1.—Polarographic behavior of the cathode solution during electrolysis at a cathode potential of −1.2 to −1.4 V (sce).

It was the polarographic behavior of the tetrabromide I (two 2-electron waves at −1.8 and −2.3 V) which led us to believe that its reduction proceeds in a stepwise manner to yield spiropentane through the intermediate V. It was thus concluded that if



the reduction of I is carried out at a controlled potential the isolation of V would be possible. This was indeed verified experimentally as the reduction of I at a cathode potential of −1.2 to −1.4 V (sce) yielded compound V and the reduction of V at a potential of −2.2 V (sce) yielded spiropentane. Furthermore, the course of the reduction was easily followed by examining the polarographic behavior of the cathode solution in the macroscale reduction. Thus, in the formation of compound V, the intensity of the polarographic wave with $E_{1/2}$ = −1.8 V (sce) decreased with time while that of the wave with $E_{1/2}$ = −2.3 V did not change (Figure 1). Compound V exhibits one 2-electron polarographic wave with $E_{1/2}$ at −1.8 V (sce). Thus, its reduction was easily followed by observing the decrease of the intensity of this wave with time.

The isolation of the previously undetected intermediate V from the reduction of I demonstrates the merit of CPE in conjunction with polarography. It is believed that CPE represents a powerful tool for the elucidation of certain organic reactions as well as the synthesis of organic compounds. The synthesis of V by conventional methods[8] involves four steps while the current method requires only one.

Experimental Section

Polarographic Studies.—All polarograms were measured on a Beckman electroscan-30. A saturated calomel electrode (sce) was used as the reference. A solution of 0.05 *N* *n*-Bu_4NClO_4

(1) M. R. Rifi, *J. Amer. Chem. Soc.*, **89**, 4442 (1967).
(2) M. R. Rifi, *Tetrahedron Lett.*, 1043 (1969).
(3) M. R. Rifi, *Collect. Czech. Chem. Commun.*, **36**, 932 (1971).
(4) D. E. Applequist, *J. Org. Chem.*, **23**, 1715 (1958).
(5) H. O. House, R. C. Lord, and H. S. Rao, *ibid.*, **21**, 1487 (1956).
(6) V. A. Slabey, *J. Amer. Chem. Soc.*, **68**, 1335 (1946).
(7) F. Covitz, unpublished results.
(8) M. Slobodin and I. N. Shokhar, *J. Gen. Chem. USSR*, **21**, 2231 (1951).

(polarographic grade, Matheson Coleman and Bell) in dimethylformamide (reagent grade) was used for all measurements. The tetrabromide I exhibited two 2-electron waves at −1.8 and −2.33 V (sce), while compound V exhibited one 2-electron wave at −2.33 V (sce).

Macroscale Electrolysis. Preparation of Compound V.—The electrolysis cell used for controlled potential electrolysis was described in a previous article.[1] Compound I (25 g, 0.06 mol) in 200 ml of 0.05 *N* *n*-Bu_4NClO_4 in DMF was electrolyzed at a mercury cathode at room temperature. The potential of the cathode varied between −1.2 and −1.4 V (sce). The overall voltage was 80 V and allowed the passage of 0.3 A through the cell.[9] The course of the reaction was followed polarographically (see Figure 1). At the conclusion of electrolysis, as indicated by the near disappearance of the first wave,[10] no product had collected in the trap. Distillation at atmospheric pressure did not afford any low-boiling material. The product was hydrolyzed with 200 ml of water and extracted into 500 ml of pentane. The pentane layer was distilled at atmospheric pressure to give 7.8 g of a slightly yellowish liquid which was distilled at reduced pressure 63° (7 mm) [reported[8] for V, bp 83–87° (22 mm)] to give 6.9 g of V. The identity of V was arrived at from its nmr spectrum (CCl_4) which exhibited two singlets of equal areas at 0.92 and 3.45 ppm (spiropentane and compound I exhibit one singlet each at 0.75 and 3.52 ppm, respectively) and from its elemental analysis. *Anal.* Calcd for $C_5H_8Br_2$: C, 26.34; H, 3.54; Br, 70.17. Found: C, 26.6; H, 3.63; Br, 70.10.

Preparation of Spiropentane from Compound V.—The reduction of the dibromide V (11.0 g) was carried out under the same conditions described for I. The potential of the cathode was kept at −2.2 V (sce). This afforded spiropentane (1.3 g) which was identified from its nmr spectrum (CCl_4) which exhibited a singlet at 0.75 ppm.

Registry No.—I, 3229-00-3; V, 29086-41-7.

(9) Under these conditions enough heat is generated to boil spiropentane and similar products; hence, a Dry Ice–acetone trap was connected to the cathode compartment.

(10) Further electrolysis may cause the formation of spiropentane.

A Facile Reduction of Unsaturated Compounds Containing Oxygen[1]

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During the syntheses of some sesquiterpenoid natural products, we had the necessity of reducing an allylic diol to the corresponding saturated diol. We subsequently found that nickel boride catalyzed the addition of gaseous hydrogen to the π bond quantitatively in 0.5 hr with no accompanying hydrogenolysis of the alcohol functions.

The catalyst, nickel boride, has been described previously.[2] The Browns[3,4] have reported two types of nickel boride catalyst (P-1, prepared in water, and P-2, prepared in ethanol) and the results of hydrogenations of many hydrocarbons over these catalysts in their own hydrogenation apparatus.

(1) Presented in part at the 50th Anniversary Meeting of the Southwestern Rocky Mountain Division of the American Association for the Advancement of Science, Las Vegas, N. M., April 1970.

(2) (a) H. I. Schlesinger and H. C. Brown, U. S. Patent 2,461,661 (1949); (b) R. Paul, P. Buisson, and N. Joseph, *Ind. Eng. Chem.*, **44**, 1006 (1952).

(3) H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, **85**, 1003, 1005 (1963).

(4) (a) C. A. Brown, *Chem. Commun.*, 952 (1969); (b) C. A. Brown, *J. Org. Chem.*, **35**, 1900 (1970).

We have hydrogenated many oxygen-containing compounds employing nickel boride in a Parr hydrogenator. All compounds, with three exceptions, gave quantitative yields of single compounds from reduction of the carbon–carbon π bond(s) only. A representative selection of the olefinic compounds hydrogenated is listed in Table I. Table II lists some acetylenic compounds that were hydrogenated and some olefin derivatives that did not undergo hydrogenation.

TABLE I

TIMES OF HYDROGENATIONS OVER NICKEL BORIDE

Compd	Time[a]
Diallyl ether	20 min[b]
Allyl alcohol	30 min
2-Butene-1,4-diol (cis)	1 hr
Cinnamyl alcohol (trans)	3 hr
2-Cyclopentene-1,4-diol	30 min
1-Phenyl-2-propenol	8 min
Cinnamaldehyde (trans)	24 hr[c]
5-Hexen-2-one	12 min
Mesityl oxide	6.75 hr
Allyl acetate	16 min
Ethyl cinnamate	2 hr
Cinnamic acid (trans)	*d*
Maleic acid	1 hr

[a] Time required for the uptake of 1 equiv of hydrogen. [b] Time required for the uptake of 2 equiv of hydrogen. [c] Half reaction. [d] No hydrogen uptake after 37 hr.

TABLE II

OTHER COMPOUNDS TREATED WITH NICKEL BORIDE

Compd	Reaction time, hr
2-Butyne-1,4-diol	7.25[a]
2-Methyl-3-butyn-2-ol	1[a]
1-Ethynylcyclohexanol	*b*
Propargyl acetate	*b*
1,2-Epoxybutane	20[c]
2-Methyl-1,2-epoxypropane	20[c]

[a] Time required for the uptake of 2 equiv of hydrogen. [b] Not available: data supplied by Dr. C. A. Brown, private communication [c] No hydrogen uptake.

The reaction products of the compounds listed were isolated by gas chromatographic techniques and identified by spectral methods. No products resulting from either hydrogenation or hydrogenolysis of the functional groups were detected by gas chromatography. Also, no further uptake of hydrogen was observed for any of the compounds listed following the uptake of the calculated amount.

The results of the hydrogenations of the π bonds are similar to results indicated by Polkovnikov, *et al.*,[5] for three other borohydride-reduced metals. They reported times for the uptake of equivalents of hydrogen by cyclopentadiene, cyclohexene, cinnamaldehyde, crotonaldehyde, and dimethyl maleate using platinum, palladium, and rhodium borides. However, they reported no products.

The compounds that did not undergo hydrogenation did not deactivate the catalyst. After attempting to hydrogenate each one, allyl alcohol was added to the

(5) B. D. Polkovnikov, A. A. Balandin, and A. M. Taber, *Dokl. Akad. Nauk SSSR*, **145**, 809 (1962).

hydrogenation flask and the flask was reconnected to the hydrogenator. Propyl alcohol was obtained quantitatively in less than 0.5 hr from each experiment with cinnamic acid and the butylene oxides. Also, the epoxides were not rearranged to carbonyl compounds by the catalyst.

The catalyst is exceedingly simple to prepare and use. It may be prepared in the hydrogenation flask directly or in larger quantities in a centrifuge flask. The catalyst may be isolated by centrifuging the flask, stored indefinitely under nitrogen, either dry or under ethanol, and used as needed.

The results indicate that nickel boride has a great utility in the syntheses of complex organic compounds, not just for the reduction of olefins or acetylenes. While other materials have been reported[6] capable of catalyzing these conversions, nickel boride has not been found to catalyze rearrangements, hydrogenolyses, or carbonyl reductions which can accompany catalytic hydrogenations. We are currently studying the hydrogenation of nitrogen-containing compounds and the use of aprotic solvents to extend the applications of nickel boride.

Experimental Section

Chemicals.—2-Butene-1,4-diol and 2-butyne-1,4-diol were supplied by Antara Chemical Co. 2-Cyclopentene-1,4-diol was prepared by the method of Owen and Smith.[7] 1-Phenyl-2-propenol was prepared by the method of Braude, *et al.*[8] Maleic acid was prepared from the anhydride by the method of Vogel.[9] Cinnamaldehyde was extracted with dilute sodium bicarbonate solution to remove any acid present. Cinnamic acid was converted to the sodium salt which was dissolved in water and extracted with benzene, chloroform, and ether. Addition of gaseous hydrogen chloride precipitated cinnamic acid from the aqueous solution. All other compounds were used from the bottles with no purification.

Catalyst Preparation.—For a single hydrogenation, 1.24 g (5 mmol) of powdered nickel acetate, 50 ml of 95% ethanol, and a short spinbar are placed in the hydrogenation flask. Stirring is begun and the flask flushed with hydrogen. Injection of 5 ml of 1.0 *M* sodium borohydride into the flask produces the black colloidal catalyst.

For the bulk catalyst, the above procedure is followed using larger amounts of nickel acetate and sodium borohydride solutions and a large centrifuge tube. The colloidal catalyst is easily separated from the solution by centrifuging at 3000 rpm for several minutes. The isolated catalyst can be stored under nitrogen indefinitely, either dry or under ethanol.

Hydrogenation Procedure.—To the catalyst and preparatory solutions in the hydrogenation flask is added 10 mmol of the compound to be hydrogenated, neat if liquid or dissolved in a minimum amount of ethanol if solid. If the preprepared catalyst is used, the compound is added to 50 mg of the catalyst in 50 ml of 95% ethanol. The flask is then connected to the Parr hydrogenator and shaken until the theoretical pressure drop for hydrogen is observed. Initial hydrogen pressure was 30 psi in all experiments. The contents of the hydrogenation flask are then centrifuged to separate the catalyst. The decantate was analyzed by gas chromatography. All reaction products were collected and identified by comparison of infrared spectra with those of authentic samples.

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(6) See, *inter alia*, P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, N. Y., 1967, and references therein.

(7) L. N. Owen and P. N. Smith, *J. Chem. Soc.*, 4043 (1952).

(8) E. A. Braude, E. R. H. Jones, and E. S. Stern, *ibid.*, 396 (1946).

(9) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1956, pp 462–463.

Oxidation of *meso*-Tetraphenylchlorins by Dimethyl Sulfoxide to the Corresponding *meso*-Porphyrins[1]

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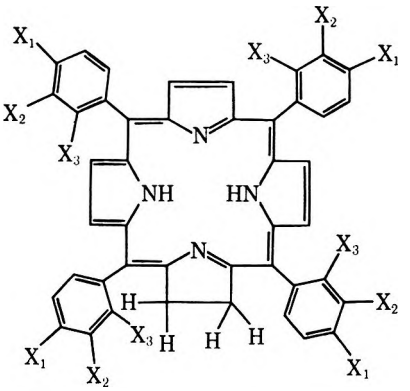
Various meso-tetrasubstituted porphins are prepared by Rothemund synthesis[3–9] but rarely are they obtained chlorin-free.[6] Calvin, *et al.*,[4] separated *meso*-tetraphenylporphin (TTP) from *meso*-tetraphenylchlorin (TPC) by chromatography over talc. This method was later used for purification of similar porphyrins.[8,9] Partial oxidation of chlorins has been achieved with quinones,[10] and selective photooxidative decomposition of zinc chlorins in benzene solution in the presence of quinones followed by chromatography gave pure zinc porphyrins.[9,11] However, these methods of



1, $X_1 = X_2 = X_3 = H$
2, $X_2 = X_3 = H$; $X_1 = CH_3$
3, $X_2 = X_3 = H$; $X_1 = OCH_3$
4, $X_1 = X_3 = H$; $X_2 = OCH_3$
5, $X_1 = X_2 = H$; $X_3 = OCH_3$
6, $X_2 = X_3 = H$; $X_1 = CN$
7, $X_2 = H_3 = H$; $X_1 = NHCOCH_3$

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(2) Undergraduate Research Participant.

(3) P. Rothemund, *J. Amer. Chem. Soc.*, **63**, 267 (1941).

(4) M. Calvin, R. H. Ball, and S. Aronoff, *ibid.*, **65**, 2259 (1943); R. H. Ball, G. D. Dorough, and M. Calvin, *ibid.*, **68**, 2279 (1946).

(5) A. D. Adler, F. R. Longo, and J. D. Finarelli, *ibid.*, **86**, 3145 (1964); A. D. Adler, F. R. Longo, J. D. Finarelli, J. Goldmacher, J. Assour, and L. Korsakoff, *J. Org. Chem.*, **32**, 476 (1967).

(6) N. Datta-Gupta and T. J. Bardos, *J. Heterocycl. Chem.*, **3**, 495 (1966).

(7) A. D. Adler, L. Sklar, F. R. Longo, J. D. Finarelli, and M. C. Finarelli, *ibid.*, **5**, 669 (1968).

(8) D. W. Thomas and A. E. Martell, *J. Amer. Chem. Soc.*, **78**, 1335 (1956).

(9) G. M. Badger, R. Alan Jones, and R. L. Laslett, *Aust. J. Chem.*, **17**, 1022 (1964).

(10) V. Eisner and R. P. Linstead, *J. Chem. Soc.*, 3749 (1955).

(11) F. M. Huennekans and M. Calvin, *J. Amer. Chem. Soc.*, **71**, 4031 (1949).

TABLE I
ELECTRONIC ABSORPTION SPECTRA OF *meso*-PORPHYRINS TAKEN IN BENZENE SOLUTION[a]

	λ_{max}, mμ (ε × 10^{-3})					
Compd	Soret	IV[b]	III[b]	II[b]	Ia[b]	Ib[b]
1[c]	420 (450)	484 (5.0)	516 (20.7)	550 (8.5)	592 (5.8)	646 (3.8)
1[d]	419 (438)	484 (3.8)	516 (18.4)	549 (8.3)	594 (5.1)	652 (7.4)
1[e]	419 (470)	485 (3.4)	514 (18.7)	549 (7.7)	591 (5.4)	647 (3.4)
1[f]	419 (478)	485 (3.4)	514 (18.7)	548 (8.1)	592 (5.3)	647 (3.5)
1[g]			515 (19.0)	548 (8.0)	592 (5.2)	647 (3.5)
2[c]	420 (558)	483 (6.0)	516 (23.0)	551 (12.0)	594 (6.9)	649 (5.8)
2[d]	421 (478)	484 (5.6)	517 (21.8)	550 (12.6)	595 (6.4)	652 (15.4)
2[f]	420 (490)	485 (3.7)	516 (18.9)	550 (8.2)	592 (5.4)	650 (4.1)
2[h]	420 (485)	485 (4.2)	516 (19.0)	550 (9.7)	592 (5.4)	650 (4.4)
3[c]	423 (410)	486 (4.8)	519 (15.6)	556 (10.2)	596 (5.0)	650 (4.6)
3[d]	424 (385)	488 (3.4)	521 (14.5)	557 (9.7)	598 (4.1)	652 (6.5)
3[e]	424 (408)	488 (3.4)	518 (13.5)	556 (8.9)	595 (4.0)	652 (3.7)
3[f]	424 (485)	488 (4.3)	519 (17.0)	555 (11.9)	595 (5.5)	653 (4.5)
4[c]	422 (480)	485 (5.4)	518 (22.0)	552 (8.1)	594 (6.5)	648 (3.5)
4[d]	420 (357)	483 (3.4)	515 (16.8)	549 (6.5)	594 (4.7)	643 (6.6)
5[c]	421 (568)	482 (7.3)	515 (26.8)	549 (10)	592 (8.3)	648 (4.7)
5[d]	424 (518)	486 (5.2)	518 (19.4)	554 (13)	595 (5.8)	650 (8.6)
5[e]	420 (349)		513 (15.2)	546 (4.6)	590 (4.2)	647 (1.5)

[a] Because of difficulty of solution, compounds **3** and **5** were dissolved initially in pyridine, 0.1 ml for 1 mg of the substance. [b] Numbering of visible absorption bands was done according to J. E. Falk, "Porphyrins and Metaloporphyrins," Elsevier, Amsterdam, London, New York, 1964." [c] Porphyrins purified by the present method. [d] Impure porphyrins obtained by the Rothemund synthesis. [e] From ref 9. [f] From ref 8. [g] From ref 4. [h] From ref 6.

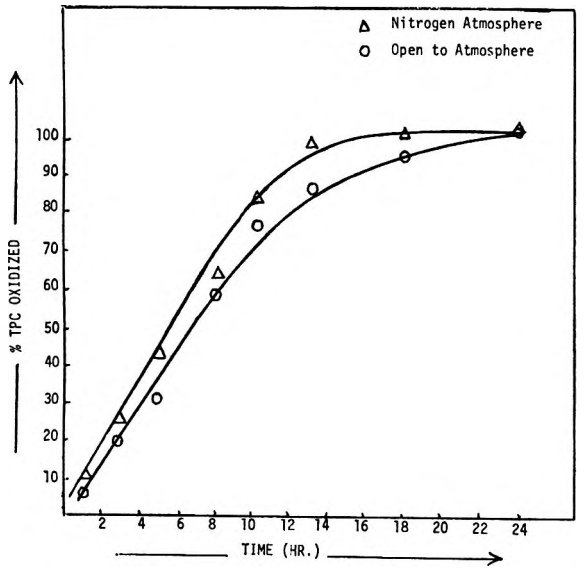


Figure 1.—Rate of oxidation of TPC in boiling DMSO.

obtaining chlorin-free porphyrins are very tedious and time consuming.

This work reports the convenient and quantitative oxidation of several *meso*-chlorins **1–7** in boiling dimethyl sulfoxide (abbreviated as DMSO) to the corresponding *meso*-porphyrins. Spectroscopic measurements show that the *meso*-porphyrins obtained by this method are purer than those obtained by the most reliable chromatographic separation.

Chlorins **1–7** are present as impurities [as high as 10% in the case of TPC (**1**)] in the corresponding porphyrins prepared by the Rothemund synthesis.[5,6] Porphyrins corresponding to chlorins **5** and **7** are new.[12]

Experimental Section

All the solvents used in this work were reagent grade, however, the DMSO was specially purified to free it from any dimethyl sulfone.[13] For spectral measurements a Perkin-Elmer Model 202 ultraviolet–visible absorption spectrophotometer was used. The molar absorbances of pure TPP and pure TPC were obtained from the literature.[4,14] The absorbances at 515 and 650 mμ were used to calculate the per cent of TPP as well as TPC in the reaction mixtures.[15]

Oxidation of *meso*-Chlorins.—*meso*-Porphyrins containing *meso*-chlorins, 0.1 g, were suspended in 100 ml of DMSO and refluxed for 18–24 hr. At different times aliquots of the reaction mixture were diluted with pyridine and the visible absorption spectra were determined. When the intensity of the absorption band near 650 mμ became weaker than the band near 590 mμ and the ratio of the intensity of absorptions at 515–650 mμ remained the same in two successive measurements, the refluxing was discontinued and the porphyrin isolated. The electronic absorption spectra in benzene solution of pure and impure *meso*-porphyrins corresponding to the *meso*-chlorins **1–5** are given in Table I. Spectral data obtained from the literature for porphyrins corresponding to chlorins **1**, **2**, **3**, and **5** are included in this table for comparison.

Effect of Oxygen on the Oxidation of TPC to TPP.—Two experiments were carried out for this. In the first experiment 200 mg of TPP (containing 10% TPC) was refluxed for 24 hr in 200 ml of DMSO (sulfone free) open to the atmosphere. Aliquots of the reaction mixture were periodically taken and the amount of TPC was determined spectrophotometrically. In the second experiment everything was the same except the reaction was carried out under nitrogen atmosphere.[16] The sulfone-free DMSO (100 ml) was freed from dissolved oxygen by bubbling oxygen-free nitrogen for 30 min at 100° and to this was carefully introduced 200 mg of impure TPP and refluxed under nitrogen atmosphere.[16] Aliquots of the reaction mixture were removed also under nitrogen atmosphere for spectral measurements. These operations were done in an all-glass apparatus.

Figure 1 shows the effect of air and nitrogen on the rate of oxidation of TPC by DMSO. It is apparent that atmospheric oxygen is not required for the oxidation.

(12) The synthesis of porphyrins corresponding to chlorins **5** and **7** will be published later.

(13) The DMSO was treated with Atlas Corporation's Darco G-60 (1% for 30 min at room temperature), filtered, and distilled with a fractionating column under nitrogen atmosphere. The final 25% residue was rejected. This method has been obtained by private communication with Crown Zellerbach Corp., Chemical Products Division, Camas, Wash.

(14) G. D. Dorough and F. M. Hunnekans, *J. Amer. Chem. Soc.*, **74**, 3974 (1952).

(15) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy" Wiley, New York, N. Y., 1962, Chapter 20, pp 557–558.

(16) Nitrogen gas of highest purity was freed from trace oxygen by first passing it through a solution of lithium aluminum hydride and benzopinacolone in pyridine (see L. F. Fieser and M. Fieser, "Reagents for Organic Syntheses," Wiley, New York, N. Y., 1967, p 247) and then through a wash bottle containing dry DMSO.

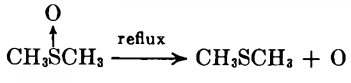
Effect of Temperature on the Oxidation of TPC to TPP.—Four independent oxidation reactions were carried out at temperatures of 150, 165, 175, and 189° (boiling point of DMSO). For each reaction 100 mg of TPP (containing up to 10% TPC) was refluxed for 24 hr in 100 ml of DMSO. The TPP that was isolated from the 175 and 189° reaction did not contain any TPC. The reaction at 165° gave only partial oxidation of TPC and the 150° reaction produced no effect. It was also observed that DMSO decomposed rapidly at 175 and 189°, slowly at 165°, and at no detectable rate at 150°. Therefore, DMSO decomposition is necessary for the oxidation of TPC to TPP.

Attempts to Prepare TPP in One Step. 1.—A mixture of pyrrole (freshly distilled), 0.67 g (0.01 mol), benzaldehyde (distilled), 1.06 g (0.01 mol), and dry DMSO, 100 ml, was refluxed for 48 hr. Although a very low yield of TPP was obtained, the product was completely free from TPC.

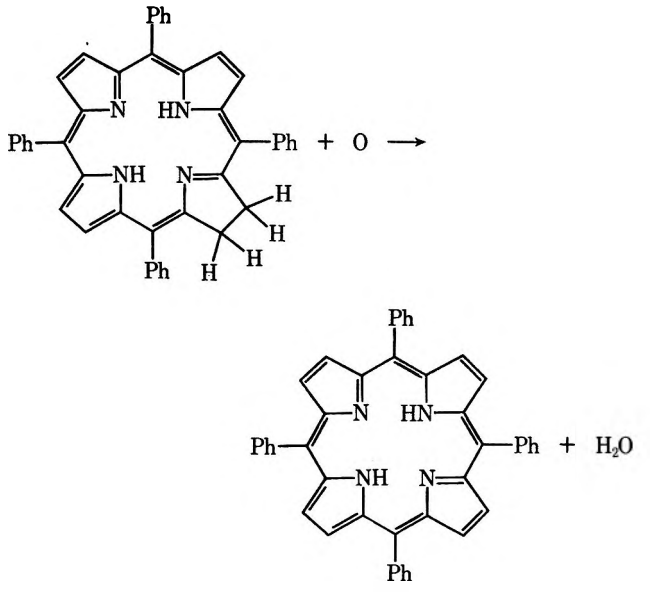
2.—A mixture of pyrrole (freshly distilled), 0.67 g (0.01 mol), benzaldehyde (distilled), 1.06 g (0.01 mol), dry DMSO, 50 ml, and propionic acid, 50 ml, was refluxed for 1 hr. There was a large degree of decomposition producing a dark polymeric product. The reaction mixture did not contain any TPP or TPC.

Discussion

It is known that DMSO decomposes at its boiling point into dimethyl sulfide and oxygen as shown below.



This oxygen atom is a powerful oxidizing agent and has been shown to take part in a number of oxidation reactions.[17] It is this reaction that is responsible for the oxidation of *meso*-chlorins to *meso*-porphyrins as shown in the following equation.



The oxidation scheme proposed above is supported by the already mentioned experiments. Attempts to fit the kinetic data (see Figure 1) to first order and second order with respect to the concentration of TPC were not successful. This may be because the rate of oxidation of TPC depends on the rate of oxidation of DMSO. The effect of temperature on the oxidation supports this view. Further studies to elucidate the mechanism of DMSO oxidation are in progress. It is important to indicate that the *meso*-porphyrins obtained by the present method are highly crystalline and purer than those obtained by other methods (see Table I) which is supported by the higher molar absorbances of *meso*-porphyrins corresponding to the chlorins **1**, **2**, **3**, and **5**.

Registry No.—**1**, 917-23-7; **2**, 14527-51-6; **3**, 22112-78-3; **4**, 29114-93-0; **5**, 29114-94-1; **6**, 22112-82-9; **7**, 22220-20-8.

(17) "Dimethylsulfoxide-Reaction Medium and Reagent," Crown Zellerbach Corp., Chemical Products Division, Camas, Wash., June 1962.

A New Synthesis of Cyclopentenones. Methyl Jasmonate and Jasmone

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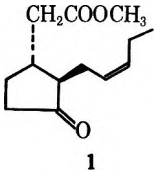
Received December 17, 1970

Methyl jasmonate (**1**),[1] a constituent of *Jasminum grandiflorum L.*, has become a valuable raw material in modern perfumery. Despite its importance its chemical synthesis has received little attention. An early synthesis[2] serving mainly to confirm the structure of the odor principle was structurally nonspecific. A more recent[3] synthesis, although elegant, proceeds through intermediates which are difficult to separate from concomitantly formed isomers.



1

We wish to describe an efficient seven-step synthesis of methyl jasmonate (**1**) from dihydroresorcinol (**2**) in 30% overall yield. It was our intention to introduce the acetic acid side chain present in the molecule by addition of a malonic ester to the cyclopentenenone **6** which, in turn, we hoped to prepare by ring contraction of a readily available derivative of cyclohexane. Of the few methods available to effect the latter transformation, the pyrolysis of 2-acetoxy-2-alkylcyclohexane-1,3-diones seemed attractive.[4,5] It proceeds in acceptable yields to give carbon monoxide and 2-alkylcyclopentenones. Unfortunately, this potentially useful method has found no applications because the acetoxydiones, prepared by oxidation of the corresponding β diketones with lead tetraacetate in yields below 20%, remain inaccessible. Although the mechanism of the thermal ring contraction of 2-acetoxy-2-alkylcyclohexane-1,3-diones remains uncertain, Spencer[4] favors the intermediacy of cyclopropanones.[6] Our hope that such cyclopropanones should also be available by elimination of hydrogen chloride from 2-chloro-2-alkylcyclohexane-

(1) E. Demole, E. Lederer, and D. Mercier, *Helv. Chim. Acta*, **45**, 675 (1962).

(2) E. Demole and M. Stoll, *ibid.*, **45**, 692 (1962).

(3) K. Sisido, S. Kurozumi, and K. Utimoto, *J. Org. Chem.*, **34**, 2661 (1969).

(4) T. A. Spencer, A. L. Hall, and C. Fordham v. Reyn, *ibid.*, **33**, 3369 (1968).

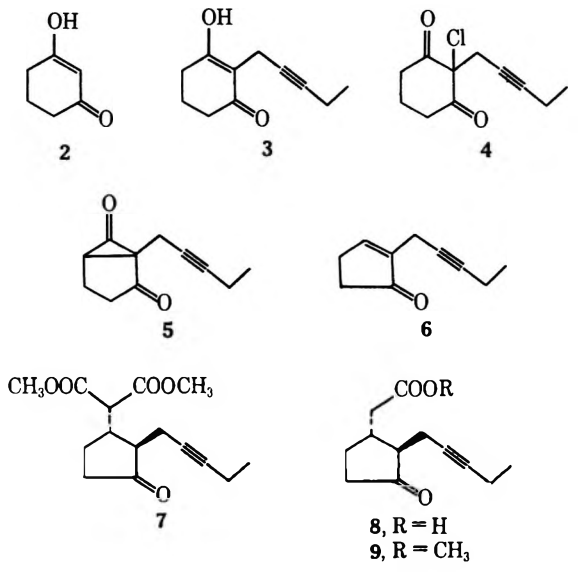
(5) T. A. Spencer, S. W. Baldwin, and K. K. Schmiegel, *ibid.*, **30**, 1294 (1965).

(6) Cyclopropanones seem to be intermediates also in the thermolysis of 2-acetoxycycloalkanones to cycloalkenes: R. G. Carlson and J. H. Bateman, *ibid.*, **32**, 1608 (1967).

1,3-diones proved correct and led to a new synthesis of cyclopentenones.

Condensation of cyclohexane-1,3-dione (2) with 1-bromo-2-pentyne in aqueous potassium hydroxide[7] yielded the crystalline C-alkylated diketone **3**. Chlorination with *tert*-butyl hypochlorite in chloroform was fast even at −15° and produced the crystalline chlorodiketone **4**. Initial efforts to eliminate hydrogen chloride from this intermediate with tertiary amines proved disappointing. The predominant product was the β diketone **3** accompanied by minor amounts of the desired cyclopentenone **6**. A systematic study aimed at finding a nonnucleophilic base not prone to accept a positive chlorine atom from the chloro diketone was then undertaken. Sodium carbonate proved to be the reagent of choice. In boiling xylene the reaction was complete within 12 hr giving the cyclopentenone **6** reproducibly in 74% yield. The gas evolved was shown to be a mixture of carbon dioxide and carbon monoxide by high resolution mass spectrometry. We assume that the cyclopropanone **5** is an intermediate and recent studies on the thermal decarbonylations of isolable cyclopropanones support this hypothesis. *trans*-2,3-Di-*tert*-butylcyclopropanone, *e.g.*, undergoes rapid decarbonylation at 150°.[8]

To continue the synthesis of methyl jasmonate, dimethyl malonate was added to the cyclopentenone **6**. Hydrolysis of the resulting diester **7** and decarboxylation to the acid **8**, followed by esterification, were all uneventful and gave methyl dehydrojasmonate (**9**). Catalytic hydrogenation of the acetylene **9** over a Lind-

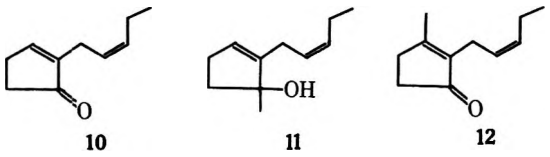


lar catalyst completed the synthesis of methyl jasmonate (**1**). Gas chromatography of material thus obtained revealed the presence of two impurities in the amounts of 1 and 3%, respectively. The mass spectra of these contaminants were indistinguishable from those of methyl jasmonate (**1**), and we suspect that they represent isomers differing in stereochemistry at the cyclopentane carbon atoms and at the double bond.

(7) Method of K. W. Rosenmund and H. Bach, *Chem. Ber.*, **94**, 2394 (1961).

(8) D. B. Sclove, J. F. Pazos, R. L. Camp, and F. D. Greene, *J. Amer. Chem. Soc.*, **92**, 7488 (1970). For other cases, see J. K. Crandall and W. H. Machleder, *ibid.*, **90**, 7347 (1968), and N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969).

The dienone **10** available by catalytic reduction of the acetylene **6** or less efficiently by hydrogenation of **3** followed by chlorination with *tert*-butyl hypochlorite and dehydrochlorination with sodium carbonate could be transformed to jasmone **12** by condensation with methyllithium and oxidation of the resulting carbinol **11** with chromium trioxide.



10 **11** **12**

Experimental Section

Microanalyses were performed at the MIT Microchemical Laboratory and in the Microanalytical Department of Firmenich et Cie, Geneva. Melting and boiling points are uncorrected. The following spectrometers were used: nuclear magnetic resonance (nmr); Varian T-60 and A-60 (peaks reported in parts per million downfield from TMS as internal standard); infrared (ir), Perkin-Elmer Model 237 and A 21; mass spectrometer (mass spectrum) Atlas CH-4; ultraviolet (uv), Cary Model 14. Vapor phase chromatography (vpc) analyses were performed on F & M 720 and Varian Aerograph 1800 instruments using silicone rubber SE 30 and Carbowax 20M columns. Thin layer chromatograms (tlc) were prepared with Merck silica gel GF 254.

2-(2-Pentynyl)-1,3-cyclohexanedione (3).—1-Bromo-2-pentyne[9] (100 g, 0.68 mol) was added to an ice-cold solution of 1,3-cyclohexandione (90 g, 0.8 mol) in potassium hydroxide (56 g, 1 mol) and water (200 ml). The reaction mixture was stirred for 15 hr at room temperature and then 3 hr at 50°. The mixture was poured into 4 *N* sodium hydroxide (500 ml) and washed twice with ether for removal of the neutral compounds. The aqueous solution was acidified with cold hydrochloric acid solution (400 g of concentrated HCl in 400 g of crushed ice). A precipitate was obtained which yielded after filtration, washing with water, and drying *in vacuo* 2-(2-pentynyl)-1,3-cyclohexanedione, 100 g (82.5%) mp 162–170°. A small sample was crystallized twice from methanol: mp 179–181°; uv (EtOH) 259 mμ (ε 15,400); ir ($CHCl_3$) 3330, 1620, 1180, 1130 cm^{-1}; nmr ($CDCl_3$) δ 1.15 (3 H, t), 1.8–2.6 (8 H, m), 3.2 (2 H, unresolved q), 8.3 (1 H, b).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.14; H, 7 79.

1-Chloro-1-(2-pentynyl)-2,6-cyclohexanedione (4).—*tert*-Butyl hypochlorite[10] (108.5 g, 1 mol) was added under a nitrogen atmosphere over a 2-hr period to a suspension of 2-(2-pentynyl)-1,3-cyclohexanedione (178 g, 1 mol) in dry chloroform (1.5 l.) at −15 to −20°. After the addition was completed the reaction mixture was stirred for 2 hr at −15°. The solvents were removed *in vacuo* to afford the crude chloride. Distillation through a small column over a few milligrams of sodium carbonate afforded pure (tlc, benzene–EtOAc 9:1, one spot) 1-chloro-1-(2-pentynyl)-2,6-cyclohexanedione, 162 g (76%), bp 105–107° (0.001 mm), which crystallized on cooling: mp 27–29°; ir ($CHCl_3$) 1745, 1720, 1320, 1010 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (3 H, t), 1.7–2.4 (4 H, m), 2.4–3.4 (6 H, m, including δ 3.0 (2 H, t)).

Anal. Calcd for $C_{11}H_{13}O_2Cl$: C, 62.11; H, 6.16. Found: C, 61.78; H, 6.20.

2-(2-Pentynyl)-2-cyclopentenone (6).—1-Chloro-1-(2-pentynyl)-2,6-cyclohexanedione (4) (80 g, 0.377 mol) in dry xylene (800 ml) was allowed to reflux in the presence of anhydrous sodium carbonate (39.2 g, 0.38 mol) until gas evolution ceased (12 hr). The reaction mixture was cooled, washed three times with water, and dried over magnesium sulfate, and the xylene was removed *in vacuo*. The residue was distilled through a Vigreux column to afford pure (2.5 m, vpc Carbowax 20M, 5% at 150°) 2-(2-pentynyl)-2-cyclopentenone (41.3 g, 74%): bp 67–68° (0.01 mm); $n^{20}D$ 1.5037; uv (EtOH) 224 mμ (ε 6600); ir ($CHCl_3$) 3050, 1700, 1638, 1360, 1035, 1000, 790 cm^{-1}; nmr (CCl_4) δ 1.13 (3 H, t), 1.8–2.7 (6 H, m), 2.9 (2 H, q), 7.4 (1 H, m); mass spectrum *m/e* (rel intensity) 148 (80), 133 (100), 105 (44.6), 91 (97).

(9) T. Yoshida, A. Yamaguchi, and A. Komatsu, *Agr. Biol. Chem.* (*Tokyo*), **30**, 370 (1966).

(10) H. M. Teeter and E. W. Bell, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 125.

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 80.81; H, 8.13.

3-Dimethylmalonyl-2-(2-pentynyl)cyclopentanone (7).—2-(2-Pentynyl)-2-cyclopentenone (59.2 g, 0.4 mol) in dry methanol (50 ml) was added in a nitrogen atmosphere over a 0.5-hr period at −5° to a solution of dry methanol (200 ml), sodium metal (1.15 g, 0.05 g-atom), and dimethyl malonate (66 g, 0.5 mol). After the reaction mixture had been stirred for 1 hr at −5°, acetic acid (6 g, 0.1 mol) was added and the solvent removed *in vacuo*. The residue was extracted twice with ether, the organic layers were washed with water and dried over magnesium sulfate, and the ether was removed *in vacuo*. Distillation through a small Vigreux column afforded the pure (1.5 m, vpc, silicone rubber SE-30, 10%, 225°) Michael adduct: 107 g (95.5%); bp 140–145° (0.01 mm); $n^{23}D$ 1.800; ir (liquid) 3460, 1735, 1430, 1165 cm^{-1}; nmr (CCl_4) δ 1.08 (3 H, t), 1.5–2.5 (10 H, m), 3.65 (2 H, d), 3.72 (6 H, s); mass spectrum *m/e* (rel intensity) 280 (0.1), 251 (17.7), 148 (100), 133 (48), 122 (36), 107 (26.3).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.00; H, 7.29.

Dehydrojasmonic Acid (8).—Sodium hydroxide (32 g, 0.8 mol) dissolved in water (320 ml) was added slowly under a nitrogen atmosphere to the malonate 7 (107 g, 0.382 mol) at 15° over 3 hr. The reaction mixture was stirred overnight at room temperature. By extraction with ether, pure 2-(2-pentynyl)-2-cyclopentenone (3 g, 5.3%) (retro-Michael product) was removed from the reaction mixture. The aqueous solution was acidified with sulfuric acid (50 g, 0.5 mol) in water (100 ml) and heated at reflux until gas evolution ceased (3–4 hr). After two extractions with ether, the organic layers were washed with water and dried over magnesium sulfate, and the solvent was removed *in vacuo*. Distillation through a small Vigreux column afforded pure dehydrojasmonic acid:[2] 63.6 g (80%); bp 155–160° (0.01 mm); $n^{23}D$ 1.4895; ir (liquid) 3150, 2670, 1735, 1705 cm^{-1}; nmr (CCl_4 + $CDCl_3$) δ 1.09 (3 H, t), 1.8–3.1 (10 H, m), 8.6 (1 H, s); mass spectrum *m/e* (rel intensity) 208 (0.1), 179 (29), 122 (100), 107 (54).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.76; H, 7.81.

Racemic Methyl Dehydrojasmonate (9).—Dehydrojasmonic acid (8) (63.6 g, 0.306 mol) and dry methanol (200 ml) in the presence of concentrated sulfuric acid (3 g) was heated at 40° for 3 hr. The reaction mixture was cooled and sodium bicarbonate (5 g) was added. Methanol was removed *in vacuo*, the residue was extracted twice with ether, the organic layers were washed with water and dried over magnesium sulfate, and the solvent was removed *in vacuo*. Distillation through a Vigreux column afforded pure (2.5 m, vpc, Carbowax 20M, 5%, 200°) methyl dehydrojasmonate:[1] 63.5 g (93.5%); bp 100–103° (0.01 mm); $n^{23}D$ 1.4779; ir (liquid) 3460, 1735 cm^{-1}; nmr (CCl_4) δ 1.09 (3 H, t), 1.7–2.9 (12 H, m), 3.63 (3 H, s); mass spectrum *m/e* (rel intensity) 222 (0.1) 193 (43.3), 122 (100), 107 (52).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.39; H, 8.36.

This compound gave a semicarbazone, mp 167–169°.

Anal. Calcd for $C_{14}H_{21}O_3N_3$: C, 60.19; H, 7.58. Found: C, 60.23; H, 7.88.

Racemic Methyl Jasmonate (1).—Methyl dehydrojasmonate (63 g, 0.284 mol) in petroleum ether (bp 50–70°, 500 ml) was hydrogenated in the presence of Lindlar[11] catalyst (1 g). After 3 hr 1 equiv of H_2 had been absorbed. Filtration, removal of the petroleum ether *in vacuo*, and distillation through a Widmer column afforded methyl jasmonate: 59.5 g (93.5%); bp 88–90° (0.01 mm); $n^{23}D$ 1.4720; ir (liquid) 3450, 1735, 1690, 703 cm^{-1}; nmr (CCl_4) δ 0.96 (3 H, t), 1.7–2.7 (14 H, m), 3.61 (3 H, s), 5.25 (1 H, m); mass spectrum *m/e* (rel intensity) 224 (36), 151 (58), 83 (100). Infrared and nmr spectra were indistinguishable from those of authentic material.[1,2]

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.52; H, 8.98.

Ketone 10.—A solution of 171 mg (1.15 mmol) of ketone 6 in 5 ml of hexane was hydrogenated in the presence of 10 mg of Lindlar[11] catalyst. Hydrogen uptake after 45 min at 20° (760 mm) was 25.5 ml (0.92 equiv). The mixture was filtered, evaporated, and distilled to yield 157 mg (91%) of ketone 10: bp ~70° (0.05 mm); ir ($CHCl_3$) 1690, 1630 cm^{-1}; nmr (CCl_4) δ 1.0 (3 H, t, J = 7 Hz), 1.5–3.0 (8 H, m), 5.4 (2 H, m), 7.2 (1 H, m); uv (EtOH) 227 mμ (ε 10,500).

(11) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.23; H, 9.50.

Jasmone (12).—To an ice-cold solution of 115 mg (0.75 mmol) of ketone 10 in 2 ml of ether was added 1 ml (1.5 mmol) of 1.5 *M* methyllithium in ether. After 10 min at room temperature the mixture was poured into cold water. It was extracted with pentane, washed with water, dried (Na_2SO_4), and evaporated to give 121 mg of alcohol 11: ir ($CHCl_3$) 3610, 3430 cm^{-1}.

The crude carbinol was dissolved in 2 ml of ether and then a solution of 80 mg of CrO_3 in 0.8 ml of aqueous 5% H_2SO_4 was added dropwise at 5°. After being stirred for 15 min at 5° water was added and the mixture was extracted with pentane. The organic layer was subsequently washed with 5% $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated to afford 113 mg of crude jasmone (12). A pure sample was obtained by vpc collection: ir ($CHCl_3$) 1685, 1640 cm^{-1}; nmr (CCl_4) δ 1.0 (3 H, t, J = 7 Hz), 2.0 (3 H, s), 2.1–2.6 (6 H, m), 2.9 (2 H, d, J = 6 Hz), 5.2 (2 H, m). Ir and nmr spectra and retention time on vpc were identical with those of an authentic[12] sample of jasmone.

Registry No.—**1**, 20073-13-6; **3**, 29119-42-4; **4**, 29119-43-5; **6**, 29119-44-6; **7**, 29119-45-7; **8**, 29119-46-8; **9**, 29119-47-9; **9** semicarbazone, 29119-48-0; **10**, 29119-49-1; **12**, 488-10-8.

Acknowledgments.—We are indebted to Firmenich et Cie., Geneva, for generous financial support. High-resolution mass spectra were measured in the National Institutes of Health supported facility at Massachusetts Institute of Technology (Grant FR 00317) under the direction of Professor K. Biemann.

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Synthesis and Stereochemistry of *syn*- and *anti-p*-Nitrophenyl Phenacyl Methylphosphonate Oxime[1]

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Studies of neighboring oxime group participation in phosphonate ester hydrolysis have been in progress in our laboratories for the past several years. We have reported[2-4] on the very large rate enhancements in the solvolytic displacement of *p*-nitrophenol exhibited by *syn-p*-nitrophenyl phenacyl methylphosphonate oxime (**1**) and *anti-p*-nitrophenyl phenacyl methylphosphonate oxime (**2**) relative to that of ethyl *p*-nitrophenyl methylphosphonate (10^9 and 10^7 times, respectively). The experimental data in these papers support hy-

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(2) C. N. Lieske, J. W. Hovanec, G. M. Steinberg, and P. Blumbergs, *Chem. Commun.*, 13 (1968).

(3) J. W. Hovanec, C. N. Lieske, G. M. Steinberg, J. N. Pikulin, A. B. Ash, and P. Blumbergs, Abstracts, 1st Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1968, p 97.

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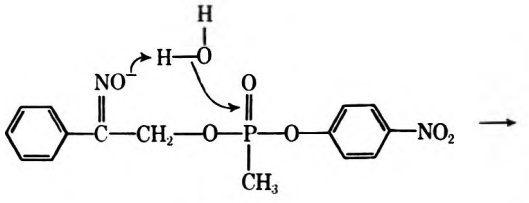
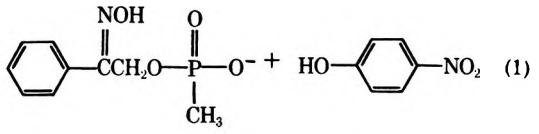
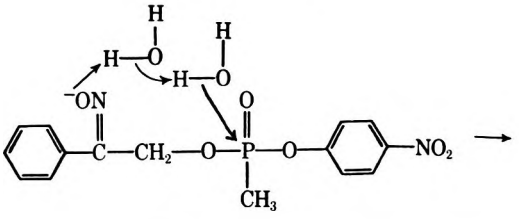
drolysis mechanisms for **1** and **2** involving oximate anion catalyzed, water-mediated reactions (eq 1 and 2).



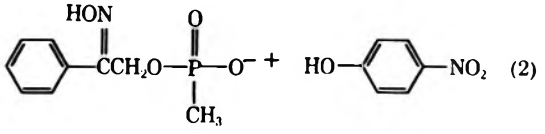
syn-**1**



(1)



anti-**2**



(2)

This paper reports the synthesis of **1** and **2**. While the isolation of **1** as a pure isomer was not achieved, a reproducible experimental procedure for *in situ* conversion of **2** to a mixture of isomers in which **1** predominates is described. Finally, from kinetic data and mechanistic considerations, assignments are made of the configurations of **1** and **2**. In light of the current controversy[5,6] in assigning oxime configurations from nmr data, the use of kinetic–mechanistic considerations, as illustrated in this work, provides a powerful tool for the stereochemical assignment of oximes in those situations where it may be invoked.

Experimental Section

General.—All melting points are uncorrected and were determined on a Hoover melting point apparatus, oil bath capillary technique, with a calibrated thermometer. Infrared spectra were recorded using a Perkin-Elmer 237B spectrophotometer. Nmr spectra were determined on a Varian A-60A spectrometer. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

***p*-Nitrophenylmethylphosphonic Acid (3).**—Bis(*p*-nitrophenyl methylphosphonate),[7] mp 121.5–122.5°, was dissolved in acetonitrile and 1.85 equiv of 1 *N* sodium hydroxide solution added over a 3-hr period. Acetic acid was added to adjust the pH to *ca.* 5. The reaction mass was diluted with water and extracted with ether until the extracts showed the absence of *p*-nitrophenol. Five extractions were usually required. The aqueous layer was acidified to pH *ca.* 2 with hydrochloric acid and extracted three times with chloroform. The combined chloroform extracts were dried and charcoaled, the solvent was removed, and the residual solid was recrystallized twice from chloroform–*n*-hexane to give a 70% yield of *p*-nitrophenylmethylphosphonic acid as white crystals, mp 111–111.5° (lit.[8] mp 90–91°).

Anal. Calcd for $C_7H_8NO_5P$: C, 38.72; H, 3.71; N, 6.45; P, 14.27. Found: C, 38.70; H, 3.70; N, 6.70; P, 14.10.

Silver Salt of *p*-Nitrophenylmethylphosphonic Acid (4).—*p*-Nitrophenylmethylphosphonic acid (2.17 g, 10 mmol) was dissolved in a minimum amount of cold distilled water. The solution was treated with powdered silver carbonate (1.88 g, 6.8 mmol) and the precipitate washed with hot water. The filtrate was lyophilized and the resulting residue washed with cold chloroform to provide 3.2 g (quantitative) of silver *p*-nitrophenyl methylphosphonate, mp 207–209°. Recrystallization from a mixture of anhydrous methanol and anhydrous diethyl ether gave white plates, mp 208–210°.

Anal. Calcd for $C_7H_7AgNO_5P$: C, 25.95; H, 2.17; P, 9.56. Found: C, 25.87; H, 2.27; P, 9.37.

Phenacyl Bromide Oxime (5).—Phenacyl bromide was dissolved in a minimum amount of methanol and treated with an aqueous solution of 1 equiv of hydroxylamine sulfate. The suspension was stirred for 1 day at room temperature and the methanol evaporated under reduced pressure. The residue was extracted with benzene and the extract dried over anhydrous sodium sulfate. The drying agent was removed by filtration. Following removal of the solvent, the residue was recrystallized from chloroform–petroleum ether (bp 30–60°) without heating. The yield was 60% (by reworking the mother liquor) of phenacyl bromide oxime, mp 97–98.5° (lit.[9] mp 97–98°). The nmr spectrum ($CDCl_3$) was as follows: δ 4.42 (s, 2, CH_2Br, 9.66 (s, 1, OH), 7.41 and 7.72 (m, 5, phenyl).

Anal. Calcd for C_8H_8BrNO: Br, 37.33. Found: Br, 37.20.

Sublimation of the oxime at 70° (0.01 mm) effected no change in melting point. Further recrystallization gave a product with mp 99–100°. The nmr spectrum was unchanged. Attempts to obtain crystals suitable for X-ray diffraction studies were unsuccessful; the crystals were fibrous in structure.

Beckmann Rearrangement of Phenacyl Bromide Oxime Using Polyphosphoric Acid (PPA).—Phosphorus pentoxide (50 g) was dissolved in 85% H_3PO_4 (32 ml). Phenacyl bromide oxime, mp 97–98.5° (0.50 g, 2.3 mmol), was added to 10 g of the PPA and the mixture was immersed in an oil bath at 135° for 5 min while stirring manually. The reaction mass was poured over cracked ice and the solid filtered to provide 0.41 g (82%) of α-bromoacetanilide, mp 132.5–134.5°. Admixture of this material with an authentic sample (mp 134–136°) did not depress the melting point of the latter.

Beckmann Rearrangement of Phenacyl Bromide Oxime Using Phosphorus Pentachloride in Ether.—Phosphorus pentachloride (1 g) was added portionwise to a cold solution (0°) of phenacyl bromide oxime, mp 97–98.5° (215 mg, 1 mmol), in 10 ml of anhydrous diethyl ether. The reaction mixture was allowed to come to room temperature, stirred for 48 hr, poured onto cracked ice, and extracted with diethyl ether. The ether extract was washed several times with water, dried (sodium sulfate), and evaporated under reduced pressure (aspirator) to furnish a light pink pasty mass. Crystallization from a mixture of methylene chloride and petroleum ether gave 60 mg (27%) of a light pink crystalline solid, mp 128–130°. Admixture of this compound with an authentic sample of α-bromoacetanilide did not depress the melting point of the latter.

***anti*-*p*-Nitrophenyl Phenacyl Methylphosphonate Oxime (2).**—A solution of phenacyl bromide oxime, mp 99–100° (432 mg, 2 mmol), in 10 ml of anhydrous acetonitrile was added to a solution of silver *p*-nitrophenyl methylphosphonate (649 mg, 2 mmol) in 240 ml of acetonitrile. The reaction solution was stirred for 2.5 hr and filtered. The oily residue obtained by evaporation of the filtrate was dissolved in methylene chloride and the solution filtered to remove traces of silver bromide. Removal of the solvent and two crystallizations of the residue from a mixture of methylene chloride and 30–60° petroleum ether without heating gave 420 mg (60%) of *anti*-*p*-nitrophenyl phenacyl methyl-

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(8) R. J. Withey, *Can. J. Chem.*, **47**, 4383 (1969).

(9) M. Masaki, K. Fukui, and M. Ohta, *J. Org. Chem.*, **32**, 3564 (1967).

phosphonate oxime, mp 115–117°. The nmr spectrum ($CDCl_3$) was as follows: δ 5.02 (d, 2, J = 9.5 Hz, $POCH_2$), 1.65 (d, 3, J = 18 Hz, PCH_3).

Anal. Calcd for $C_{15}H_{15}N_2O_6P$: C, 51.43; H, 4.31; N, 7.99. Found: C, 51.36; H, 4.28; N, 8.15.

***syn-* and *anti-p*-Nitrophenyl Phenacyl Methylphosphonate Oximes (1 and 2).**—A mixture of phenacyl bromide oxime, mp 99–100° (5.16 g, 24.2 mmol), and silver *p*-nitrophenyl methylphosphonate (7.8 g, 23.9 mmol) in 390 ml of anhydrous acetonitrile was stirred at room temperature for 2.5 hr and filtered through a sintered-glass funnel. The filtrate was evaporated under reduced pressure to provide an oily residue. The residue was dissolved in anhydrous methylene chloride and refiltered to remove the remaining silver bromide. The filtrate was evaporated to dryness under reduced pressure and the resulting residue recrystallized from a mixture of methyl ethyl ketone and 30–60° petroleum ether. The first crop of white crystals weighed 2.91 g (34%) and had mp 115–117.5° (designated sample A).

Anal. Calcd for $C_{15}H_{15}N_2O_6P$: C, 51.43; H, 4.31; N, 7.99; P, 8.84. Found: C, 51.39; H, 4.56; N, 7.90; P, 8.68.

The nmr spectrum ($CDCl_3$) of this sample contained two distinct pairs of doublets: δ 1.65 [d, J = 17 Hz, PCH_3) (minor)], 1.66 [d, J = 17 Hz, PCH_3 (major)], 5.02 [d, 2 (35%), J = 9.5 Hz, $POCH_2$], 5.31 [d, 2 (65%), J = 9.5 Hz, $POCH_2$].

A portion of sample A was dissolved in freshly distilled, dry acetonitrile and allowed to stand for 15 min. It was then evaporated to dryness (total time of 30 min). There was obtained a colorless oil which solidified to a white solid, mp 115–118° (designated sample B), with acceptable elemental analysis. The nmr spectrum of sample B ($CDCl_3$) indicated that isomerization had occurred during this treatment: δ 1.65 [d, J = 17 Hz, PCH_3 (major)], 1.66 [d, J = 17 Hz, PCH_3 (minor)], 5.02 [d, 2 (56%), J = 9.5 Hz, $POCH_2$], 5.31 [d, 2 (44%), J = 9.5 Hz, $POCH_2$]. In addition to the first crop (sample A), 2.91 g of a second crop with mp 111–116.5° (designated sample C) was isolated which contained only the upfield (δ 5.02) isomer. Further, the original sample A, after standing 10 days in the solid state, contained only the upfield (δ 5.02) isomer. As discussed in the text, the upfield isomer is assigned the anti configuration 2 and the downfield isomer is assigned the syn configuration 1.

Isomerization of 2 to 1 by Glacial Acetic Acid.—The following *in situ* isomerization of 2 to a mixture of 1 and 2 in the ratio of 3 to 1 was found to be consistently reproducible and without accompanying decomposition. In a typical experiment, 5.58 mg of 2 was dissolved in 450 μl of glacial acetic acid (Pioneer Chemical Co., Long Island City, N. Y.). The extent of isomerization was measured by a spectrophotometric kinetic procedure (see Results and Discussion) and found to reach a maximum of 75% conversion to 1 within 15 min.

Results and Discussion

The original synthesis of phenacyl bromide oxime, mp 89.5°, was accomplished by Korten and Scholl[10] in 1901 using phenacyl bromide and hydroxylamine hydrochloride. The Beckmann rearrangement, using phosphorus pentachloride in ether, gave α-bromoacetanilide. Korten and Scholl drew the structure as anti (syn phenyl), whereas present-day interpretation of the Beckmann reaction would lead to a syn (anti phenyl) assignment.[11] Fischer and Grob[12] in 1962 repeated the synthesis of Korten and Scholl to obtain phenacyl bromide oxime, mp 91°. Based on ultraviolet spectral data and metal complexing reactions of some α-dialkylaminomethyl derivatives, they also assigned the configuration as anti.

In these laboratories, the synthesis of Korten and Scholl was repeated to yield a product with mp 88.5–89°. In agreement with the recent findings of Masaki[9] and coworkers, it was found that the Korten and Scholl product contained significant quantities of phenacyl chloride oxime. Using hydroxylamine sulfate, we isolated chloride-free phenacyl bromide oxime with mp 97–98.5°. The nmr spectrum identified it as a single isomer. The Beckmann rearrangement using either phosphorus pentachloride in ether or by heating in polyphosphoric acid for 5 min at 135° gave α-bromoacetanilide (yields of 27 and 82%, respectively). These results strongly support pure phenacyl bromide oxime, mp 97–98.5°, having a syn configuration.

The synthesis of *anti-p*-nitrophenyl phenacyl methylphosphonate oxime (2) from pure phenacyl bromide oxime (5) and the silver salt of *p*-nitrophenyl methylphosphonic acid (4) was accomplished repeatedly in yields of 40–60%. The product represented a single isomer based on nmr spectral data. In a later, typical larger-scale experiment, somewhat modified (heterogeneous), 34% of a product was obtained as a first crop and shown by nmr to be a mixture of isomers consisting of 65% *syn-* and 35% *anti-p*-nitrophenyl phenacyl methylphosphonate oxime. A portion was dissolved in dry acetonitrile. The solvent was removed and the product now contained 44% syn and 56% anti oxime. Furthermore, the first crop, after standing for 10 days in the solid state, was reexamined by nmr and found to contain only the anti isomer. Clearly, the upfield isomer (anti), where there is no opportunity for hydrogen bonding between the oximino proton and the phosphoryl oxygen, is the thermodynamically more stable isomer. This observation is consistent with the results of Cherry[13] and coworkers. They found that the internally hydrogen bonded syn isomer of 3-hydroximinocamphor was less stable than the anti form.

Controlled and reproducible isomerization of the more stable upfield isomer of *p*-nitrophenyl phenacyl methylphosphonate oxime (2) to a mixture containing 75% of the downfield isomer 1 and 25% of the upfield isomer 2 was accomplished by dissolving 2 in glacial acetic acid at room temperature. Less reproducible was the thermal isomerization of 2 to 1 in deuteriochloroform at ambient temperature catalyzed by DCl–D_2O.

These conversions, established in the latter two cases by nmr spectral measurements, were confirmed by solvolysis rate studies (the hydrolysis rates of the isomers were independent of the isomerization procedure used) reinforced with supporting stoichiometric *p*-nitrophenol production. That is, spectrophotometric kinetic analysis of the isomer mixtures at the appropriate pH reflected *p*-nitrophenol production corresponding to the same percentage of the isomer in the nmr analysis. These results also established unequivocally that an isomerization step is not involved in the hydrolysis reaction. Such a diagnostic tool was made possible, of course, only by the fortuitous 100-fold difference in hydrolysis rates of the two isomers. The upfield isomer 2, which has a half-life of 1.34 min at pH 4.90 (25°)[2] is virtually inert at pH 2.48 (25°), where the lower field isomer 1 has a half-life of 2.72 min.[4] As the kinetic and mechanistic data accumulated on the two isomers[2–4] excludes mechanistic pathways other than an oximate–anion, water-mediated reaction, correlation of the nmr data and the hydrolysis rate data identifies the upfield isomer as *anti-p*-nitrophenyl phenacyl methylphosphonate oxime (2) and the downfield isomer

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(11) L. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 4 (1960).
(12) H. P. Fischer and C. A. Grob, *Helv. Chim. Acta*, **45**, 2528 (1962).
(13) P. C. Cherry, W. R. T. Cotthrell, G. D. Meakins, and E. E. Richards, *J. Chem. Soc. C*, 459 (1968).

as *syn*-*p*-nitrophenyl phenacyl methylphosphonate oxime (1). Reversal of these assignments, resulting in the anti isomer hydrolysis rate exceeding the syn isomer hydrolysis rate, would be, to the knowledge of the authors, without published precedent. In view of the current controversy[5,6] surrounding the assignment of oxime configurations from nmr data alone, the value of kinetic data and mechanistic considerations has been demonstrated. While not as universally applicable or as readily obtainable as nmr data, it does represent a useful approach in those situations where it may be invoked. To a limited extent, it is related to Meisenheimer's[14] elucidation of the configuration of ketoximes and to the work of Brady and Bishop[15] with aldoximes. In a larger sense, it is sufficiently different to offer future workers in the field of oxime configuration additional latitude in their approach to the problem of configurational assignment.

Registry No.—**1**, 25273-22-7; **2**, 25273-21-6; **4**, 29119-53-7; **5**, 14181-72-7.

(14) J. Meisenheimer, *Chem. Ber.*, **54**, 3206 (1921).
(15) O. L. Brady and G. Bishop, *J. Chem. Soc.*, 1357 (1925).

Cyanomethylidenebis(triphenylphosphonium) Dibromide. Its Use in a Convenient Modification of the Wittig Reaction

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In the course of some studies on dibromoacetonitrile, we discovered a convenient modification of the Wittig[2] reaction that affords unsaturated nitriles in generally good yields.

Dibromoacetonitrile reacted with triphenylphosphine in benzene to produce the bisphosphonium salt I. Although somewhat little studied, bisphosphonium salts such as I have been reported before.[3] It is of passing

$$Br_2CHCN + PPh_3 \xrightarrow[\text{heat}]{\text{benzene}} Ph_3\overset{+}{P}CH\overset{+}{P}Ph_3\ 2Br^- \quad (\text{I: } CN)$$

$$I + Ar(R)CHO \xrightarrow[\text{PhH, } H_2O, \text{ heat}]{\text{NaOH}} Ar(R)CH{=}CHCN + 2Ph_3PO$$

interest that trisphosphonium salts were reported long ago by Hofmann.[4] The report was incorrect, however, and trisphosphonium salts remain unknown.[5]

(1) Taken from the M.S. Thesis of A. J. H., Loyola University of Chicago, 1970.
(2) G. Wittig, *Pure Appl. Chem.*, **9**, 245 (1964), A. Maerker, *Org. React.*, **14**, 270 (1965), and A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, are recent reviews of this process.
(3) F. Ramirez, N. B. Desai, B. Hansen, and N. McKelvie, *J. Amer. Chem. Soc.*, **83**, 3539 (1961); C. N. Matthews, J. S. Driscoll, J. E. Harris, and R. J. Wineman, *ibid.*, **84**, 4349 (1962); J. S. Driscoll, D. W. Grisley, Jr., J. E. Pustinger, J. E. Harris, and C. N. Matthews, *J. Org. Chem.*, **29**, 2427 (1964).
(4) A. W. Hofmann, *Proc. Roy. Soc., London*, **10**, 189 (1860).
(5) *Cf.* G. H. Birum and C. N. Matthews, *J. Amer. Chem. Soc.*, **88**, 4198 (1966).

When I, together with an appropriate aldehyde, was refluxed with sodium hydroxide in a benzene–water solvent, the unsaturated nitrile and triphenylphosphine oxide resulted.

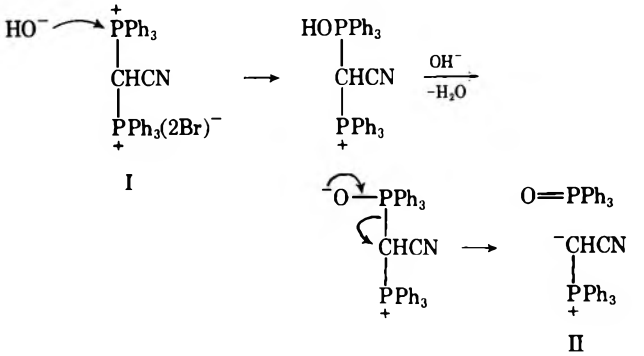
The reaction was applied to a variety of available aldehydes with the results given in Table I. Cyclohexanone failed to undergo the reaction, as might be anticipated because ketones normally fail to react with cyano-stabilized ylides.[6]

TABLE I

Starting aldehyde[a]	Isolated yield of nitrile, %	Trans:cis, %[b]
Benzaldehyde	84.7	74:26
p-Nitrobenzaldehyde	80.7	All trans
p-Isopropylbenzaldehyde	73.3	61:39
p-Methoxybenzaldehyde	72.9	All trans
α-Hexylcinnamaldehyde	78.2	*c*
Furfural	38.1	60:40
n-Heptaldehyde	74.1 (88:12)[d]	*c*
Isovaleraldehyde	66.6 (75:25)[d]	*c*
α-Ethylhexaldehyde	65.3[e]	*c*

[a] For experimental details, see the Experimental Section. [b] *Via* nmr spectral analysis. [c] Not determined because of complexity of the spectrum. [d] Ratio of α,β- and β,γ-unsaturated nitriles (see text). [e] All β,γ isomer.

In the aliphatic cases, the isolated product was partly or wholly isomerized to the (presumably equilibrated) β,γ-unsaturated nitrile, a well-investigated phenomenon in such systems.[7] The low yield of nitrile from furfural reflects the sensitivity of this aldehyde to hot base. Probably the somewhat lower yields in the aliphatic cases can be rationalized in this same way. Otherwise, the yields seem relatively insensitive to substituents, while the stereochemistry favors the more stable trans olefinic nitrile predominantly.[8] The pathway for this process seems clear. In the absence of aldehyde, treatment of I with aqueous sodium hydroxide produced the ylide II and triphenylphosphine oxide, possibly as



indicated. In the presence of aldehyde and the benzene cosolvent, II would be partitioned to some

(6) J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968, p 704.
(7) *Cf.* C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp 562–566.
(8) Mixtures of cis and trans products are commonly found in Wittig reactions: L. D. Bergel'son and M. M. Shemyakin, *Angew. Chem., Int. Ed. Engl.*, **3**, 250 (1964). No determination of isomeric stability was made in the present study, however, so no claim is made that the isolated nitriles represent the kinetic products. Most certainly in the aliphatic cases they do not.

extent into the benzene layer and there carry out the normal Wittig reaction. In support of this viewpoint,

$$Ar(R)CHO + Ph_3\overset{+}{P}-\overset{-}{C}HCN \xrightarrow[\text{heat}]{\text{benzene}} Ar(R)CH{=}CHCN + OPPh_3$$

independent reaction of II with benzaldehyde in hot benzene produced cinnamonitrile in the same yield and stereoisomeric composition of the two-phase reaction using I.[9]

Experimental Section

Melting and boiling points are uncorrected. The former were taken in capillary tubes in a Mel-Temp apparatus. Infrared spectra (in μ) were taken on a Perkin-Elmer Model 221 instrument. Nuclear magnetic resonance spectra (in δ units, parts per million, with TMS as internal reference) were determined on a Varian A-60A spectrometer in CCl_4 unless stated otherwise. Only significant spectral data are given. Microanalyses are by Micro-Tech Laboratories, Skokie, Ill. Aldehydes used were commercial samples purified immediately before use by distillation or recrystallization. Petroleum ether (bp 30–60°) was used throughout the work.

Cyanomethylidenebis(triphenylphosphonium) Dibromide (I).—Triphenylphosphine (Aldrich, 577 g, 2.2 mol) in benzene (1500 ml) was treated dropwise with dibromoacetonitrile[10] (218.6 g, 1.1 mol) at 30° with vigorous stirring. Salt I began to precipitate after 30 min. After 18 hr of further reaction at 45° the benzene was decanted and replaced by an equal volume of petroleum ether. The mixture was stirred 30 min and filtered to give I as a white solid: 673.4 g (93.4%); mp 268–269°; λ (KBr) 4.40 (CN); δ (DMSO) 8.30 s (CH), 7.75 m (Ar H).

Anal. Calcd for $C_{38}H_{31}NBr_2P_2$: C, 63.11; H, 4.28; Br, 22.10. Found: C, 63.14; H, 4.68; Br (Volhard determination by authors), 22.25, 22.46.

Cyanomethylenetriphenylphosphorane (II).—Sodium hydroxide (8 g, 0.2 mol) in water (100 ml) was added dropwise to a solution of I (72.31 g, 0.1 mol) in water (500 ml) at 25° with stirring. The crystalline precipitate of II was collected and recrystallized from benzene–ether: 26.7 g (88.8%); mp 196–197° (lit.[9] mp 186°); λ (KBr) 4.65 (CN); δ ($CDCl_3$) 7.7 m (CH and Ar H).

Anal. Calcd for $C_{20}H_{16}NP$: C, 79.75; H, 5.31. Found: C, 80.08; H, 5.30.

General Procedure for Use of I.—The appropriate aldehyde (75 mmol), salt I (54.2 g, 75 mmol), benzene (125 ml), and aqueous sodium hydroxide (10%, 50 ml) were refluxed (*ca.* 69°) for 18 hr (overnight). The layers were separated and the aqueous phase was extracted with petroleum ether. The extract together with further petroleum ether (100 ml) was added to the benzene layer. Triphenylphosphine oxide precipitated[11] and was separated [quantitative yield, mp and mmp (with authentic material) 155°]. The organic material was dried (Na_2SO_4) and evaporated and the residue distilled to afford the nitrile products. In the case of *p*-nitrocinnamonitrile, addition of the petroleum ether (200 ml) caused it to precipitate also. Separation from the phosphine oxide was achieved with hot toluene from which the nitrile could be recovered after filtration and chilling.

Cyclohexanone was recovered in 90.5% yield when subjected to this procedure. Ylide II with benzaldehyde in benzene (overnight reflux) gave the same results as use of I in the procedure above.

Properties of Nitriles. Cinnamonitrile: 8.2 g; bp 132–134° (12 mm) [lit.[12] bp 134–136° (12 mm)]; δ 7.37 sharp m (Ar H), 7.26 d, 5.80 d (trans HC=CH), 7.05 d, 5.40 d (cis HC=CH).

***p*-Nitrocinnamonitrile:** 10.5 g; mp 200–202° (lit.[13] mp 200°); δ ($CDCl_3$) 8.17 d, 7.52 d (Ar H, AA′BB′, J = 8 Hz), 7.40 d, 5.95 d (trans HC=CH).

***p*-Isopropylcinnamonitrile:** 9.4 g; bp 166–168° (16 mm); δ 7.6–6.8 m (Ar H), 7.20 d, 5.67 d (trans HC=CH), 7.10 d, 5.21 d (cis HC=CH), 2.83 septet (CH, J = 7 Hz), 1.21 d (CH_3CCH_3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{13}N$: C, 84.17; H, 7.64. Found: C, 84.19; H, 7.61.

***p*-Methoxycinnamonitrile:** 8.7 g; bp 165–170° (18 mm); mp 64° (lit.[9] mp 63°); δ 7.22 d, 6.75 d (Ar H, AA′BB′, J = 8 Hz), 7.12 d, 5.53 d (trans HC=CH), 3.72 s (OCH_3).

γ-Hexylcinnamylideneacetonitrile: 14 g; bp 214–216° (15 mm); δ 7.4–6.9 m (Ar H), 6.7 m (Ar CH=C), 5.48 m, 5.22 m (HC=CH),[14] 2.2 m, 1.3 m, 0.92 m (aliphatic H's).

Anal. Calcd for $C_{17}H_{21}N$: C, 85.31; H, 8.83. Found: C, 85.00; H, 8.79.

Furfurylideneacetonitrile: 3.4 g; bp 95–97° (11 mm) [lit.[15] bp 70° (6 mm)]; δ 7.8–6.5 series of sharp multiplets (furan ring H's and downfield portions of HC=CH), 5.83 d (upfield portion of trans HC=CH), 5.35 d (upfield portion of cis HC=CH).

2(3)-Nonenenitrile: 7.6 g; bp 98–100° (10 mm) [lit.[16] bp 99–100° (10 mm)]; δ 7.0–6.4 m, 5.5 m, 5.25 m (HC=CH),[14] 3.1 m (=CCH_2CN of Δ^3 isomer), 2.5–0.90 m (aliphatic H's). Integration data indicated 18% Δ^3 isomer.

5-Methyl-2(3)-hexenenitrile: 5.4 g; bp 168–170° (750 mm); δ 6.7–6.18 m, 5.84 m, 5.22–5.05 m (HC=CH),[14] 2.97 m (=CCH_2-CN of Δ^3 isomer), 2.4–0.80 m (aliphatic H's). Integration data indicated 25% Δ^3 isomer.

Anal. Calcd for $C_7H_{11}N$: C, 77.02; H, 10.14. Found: C, 77.06; H, 10.10.

4-Ethyl-3-octenenitrile: 7.4 g; bp 226–228° (752 mm); δ 5.10 t (=CH, J = 7 Hz), 2.97 d (=CCH_2CN, J = 7 Hz), 2.3–0.60 m (aliphatic H's). Integration data indicated only the unconjugated nitrile.

Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.31. Found: C, 79.35; H, 11.50.

In the aromatic cases, λ (CN) = 4.50–4.55 μ, whereas in the aliphatic cases λ (CN) = 4.48 μ. Where determined, J_{trans} for HC=CH was 16–17 Hz, whereas J_{cis} was 12–14 Hz.

Registry No.—I, 29127-76-2; II, 29127-77-3; *cis*-cinnamonitrile, 24840-05-9; *trans*-cinnamonitrile, 1885-38-7; *trans*-*p*-nitrocinnamonitrile, 29246-70-6; *cis*-*p*-isopropylcinnamonitrile, 29246-71-7; *trans*-*p*-isopropylcinnamonitrile, 29246-72-8; *trans*-*p*-methoxycinnamonitirle, 14482-11-2; γ-hexylcinnamylideneacetonitrile, 29127-81-9; *cis*-furfurylideneacetonitrile, 6137-73-1; *trans*-furfurylideneacetonitrile, 6125-63-9; 2-nonenenitrile, 29127-83-1; 3-nonenenitrile, 29246-75-1; 5-methyl-2-hexenenitrile, 29127-84-2; 5-methyl-3-hexenenitrile, 29246-76-2; 4-ethyl-3-octenenitrile, 29127-85-3.

(9) Using II otherwise prepared, G. Schiemenz and H. Englehard, *Chem. Ber.*, **94**, 578 (1961), previously prepared cinnamonitrile in this way.

(10) J. W. Wilt and J. L. Diebold, *Org. Syn.*, **38**, 16 (1958).

(11) In aliphatic cases this precipitation was slower and was completed in several hours at 25°.

(12) "Handbook of Chemistry and Physics," 48th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1967–1968, p C-254.

(13) S. Novikov and G. Shvekhgeimer, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2061 (1960).

(14) Stereochemistry was unassigned due to complexity of the spectrum.

(15) A Sugihara, *Yhkugaku Zasschi*, **86**, 527 (1966); *Chem. Abstr.*, **65**, 12193c (1966).

(16) K. v. Auwers, T. Meissner, O. Seydel, and H. Wissebach, *Justus Liebigs Ann. Chem.*, **432**, 46 (1923).

Reactions of Hydroxymethylferrocene. III. Ethers: Reaction with Grignard Reagents

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Grignard and Ritz have reported the cleavage of phenyl ethers by alkylmagnesium halides to give a

TABLE I

EXPERIMENTAL RESULTS

$C_5H_5FeC_5H_4CHROR' + R''MgX \longrightarrow C_5H_5FeC_5H_4CHRR'$

Product	R	R′	R″	X	$n^{20}D$ or mp, °C Found	$n^{20}D$ or mp, °C Lit.	Yield, %
IIa[a]	H	CH_3	CH_3	Br	1.6017	1.6011[b]	90
IIb	H	CH_3	$CH{=}CH_2$	Cl	1.5983	1.5990[c]	66[d]
IIc	H	CH_3	$CH_2CH{=}CH_2$	Br	1.5939	1.5940[c]	60
IId	H	CH_3	C_6H_5	Br	72–73	73–74[e]	85
IIe	CH_3	CH_3	C_6H_5	Br	1.6277[f]	1.6270[g]	80
IId	H	$CH_2CH{=}CH_2$	C_6H_5	Br	72–73	73–74[e]	57
IId	H	$CH(CH_3)_2$	C_6H_5	Br	73–74	73–74[e]	67

[a] C and H analyses (±0.3) for compounds IIa–IIe were also obtained as part of the characterization. [b] E. L. DeYoung, *J. Org. Chem.*, 26, 1312 (1961). [c] Reference 11. [d] 84% yield without solvent. [e] M. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, 22, 903 (1957). [f] Measured at 25°. [g] G. L. K. Hoh, W. E. McEwen, and J. Kleinberg, *J. Amer. Chem. Soc.*, 83, 3949 (1961).

variety of low-molecular-weight hydrocarbon products.[1] Several examples of cleavage of allyl ethers by Grignard reagents have been reported.[2-5] Hill has studied the cleavage of vinyl ethers,[6-8] while Mann and Stewart have described cleavage of benzyl ethers by alkyl and arylmagnesium halides.[9]

We now report the cleavage of ethers of hydroxymethylferrocene by Grignard reagents to yield the corresponding substituted alkylferrocene compounds in good yields. Heretofore the cleavage of ethers by Grignard reagents has found preparative use primarily in the dealkylation of protected aromatic hydroxyl groups which could not be cleaved conveniently with hydrogen bromide, hydrogen iodide, or alkali.[10] The reaction presently described appears to have broad use in the synthesis of α-substituted ferrocenylmethyl compounds from ferrocenylmethyl ethers, as well as certain α,α-disubstituted compounds which are not easily accessable otherwise. Generally, alkylferrocenes are prepared by acylation followed by reduction Nesmeyanov has obtained alkylferrocenes in 30–60%. yields by treatment of ferrocenylmethyl quaternary ammonium salts with Grignard reagents.[11] Indications are that Grignard reagents of all types will react with methyl ferrocenylmethyl ether to give the substituted products in 60–90% yields as shown.

$C_5H_5FeC_5H_4CHROR' + R''MgX \longrightarrow C_5H_5FeC_5H_4CHRR''$

Ia, R = H; R′ = CH_3 b, R = CH_3; R′ = CH_3

II a, R = H; R″ = CH_3
b, R = H; R″ = $CH{=}CH_2$
c, R = H; R″ = $CH_2CH{=}CH_2$
d, R = H; R″ = C_6H_5
e, R = CH_3; R″ = C_6H_5

Ethylferrocene was prepared in 90% yield by the reaction of methylmagnesium bromide with methoxymethylferrocene. Similarly, allylferrocene, 4-ferrocenyl-1-butene, and benzylferrocene were prepared from methoxymethylferrocene and vinylmagnesium chloride, allylmagnesium bromide, and phenylmagnesium bromide, respectively. In general, the reaction is done by addition of a benzene solution of the alkyl ferrocenylmethyl ether to a solution of the Grignard reagent in benzene. While the reaction of vinylmagnesium chloride with methoxymethylferrocene in benzene gave a 66% yield of allylferrocene (Table I), when the reaction was done without solvent the yield was 84%.

One particularly attractive feature of the method is the fact that pure products are obtained without crystallization, distillation, or chromatography. Another point worth noting is the unusual stability of compounds prepared in this way. The decomposition of ethylferrocene and other short-chain liquid alkylferrocenes is a well-known phenomenon recognized in these laboratories as well as elsewhere.[12,13] However, ethylferrocene prepared by treatment of methylmagnesium bromide with methoxymethylferrocene is stable at room temperature in the presence of light and air for several months. Although the thermodynamic stability is independent of the method of synthesis, factors influencing stability of specific samples may vary considerably. Low-molecular-weight liquid alkylferrocenes prepared by acylation–reduction continue to be unstable after rigorous purification while those prepared by the Grignard method are stable with no purification. Further experiments to explore this point are in progress.

Experimental Section

Melting points are uncorrected and were obtained by use of a Büchi apparatus. The experimental procedure is illustrated for the preparation of ethyl ferrocene, and a summary of experimental results is shown in Table I.

Ethylferrocene (IIa).—A solution of methylmagnesium bromide (4 ml, 3 *M* in ethyl ether, 0.012 mol) was placed in a 25-ml pear-shaped three-neck flask fitted with a nitrogen inlet tube, reflux condenser, and stirrer. The ether was replaced by adding sodium-dried benzene and distilling off the ethyl ether. A solution of methoxymethylferrocene (2.30 g, 0.01 mol in 5 ml of dry benzene) was added dropwise during 0.5 hr to the Grignard reagent at 70°. Mild refluxing occurred. Benzene (5 ml) was added and the mixture was cooled and filtered. The filtrate was washed with water and dried ($MgSO_4$). Solvent was removed under vacuum leaving pure ethylferrocene (1.93 g, 90% yield). In reactions in which phenylmagnesium bromide is used, heating

(1) V. Grignard and J. Ritz, *Bull. Soc. Chim. Fr.*, **3**, 1181 (1936); *Chem. Abstr.*, **30**, 5952 (1936).

(2) A. Luttringhaus, G. Wagner-v. Saaf, E. Sucker, and G. Borth, *Justus Liebigs Ann. Chem.*, **557**, 46 (1945); *Chem. Abstr.*, **40**, 5418 (1946).

(3) C. M. Hill, L. Haynes, D. E. Simmons, and M. E. Hill, *J. Amer. Chem. Soc.*, **75**, 5408 (1953).

(4) C. M. Hill, D. E. Simmons, and M. E. Hill, *ibid.*, **77**, 3889 (1955).

(5) C. M. Hill, L. Haynes, D. E. Simmons, and M. E. Hill, *ibid.*, **80**, 3623 (1958).

(6) C. M. Hill, R. A. Walker, and M. E. Hill, *ibid.*, **73**, 1663 (1951).

(7) C. M. Hill, G. W. Senter, L. Haynes, and M. E. Hill, *ibid.*, **76**, 4538 (1954).

(8) C. M. Hill, R. Woodberry, D. E. Simmons, M. E. Hill, and L. Haynes, *ibid.*, **80**, 4602 (1958).

(9) F. G. Mann and F. H. C. Stewart, *J. Chem. Soc.*, 4127 (1954).

(10) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, N. Y., 1954, p 1029.

(11) A. N. Nesmeyanor, E. G. Perevalova, and L. S. Shilovtseva, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 1982 (1961); *Chem. Abstr.*, **56**, 10185 (1962).

(12) M. D. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, **22**, 1016 (1957).

(13) A. N. Nesmeyanov and N. A. Vol'kenau, *Dokl. Akad. Nauk SSSR*, **107**, 262 (1956); *Chem. Abstr.*, **50**, 15519 (1956).

the final product under vacuum is necessary to remove biphenyl which is a by-product.

Allylferrocene (IIb).—A solution of vinylmagnesium chloride (0.012 mol in 6 ml of tetrahydrofuran) was added dropwise during 30 min to methoxymethylferrocene (2.3 g, 0.01 mol) at 100–120° under nitrogen with occasional stirring. Heating was continued for 2 hr. The reaction mixture was allowed to cool, taken up in ether, and filtered. The filtrate was washed with water, dried over $MgSO_4$, and filtered. Removal of solvent gave 1.9 g of analytically pure allylferrocene (84%).

Registry No.—Ia, 12153-89-8; Ib, 12512-90-2; I (R = H; R′ = $CH_2CH{=}CH_2$), 12512-91-3; I [R = H; R′ = $CH(CH_3)_2$], 12300-26-4.

The Chemistry of Cumulated Double-Bond Compounds. XII. The Reaction of Phosphonium Ylides with Benzoyl Isocyanate

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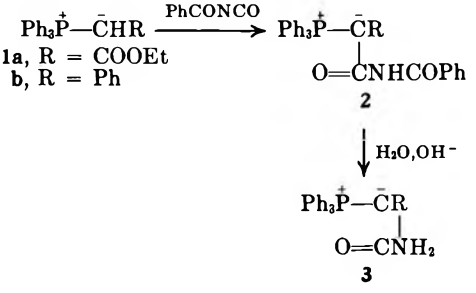
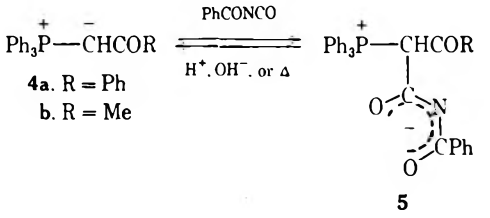
Wittig-type reactions or formation of stable ylides have been observed in the reactions between phosphonium ylides and heterocumulenes,[1-5] but reactions of ylides with acyl isocyanate have not been reported. It is well known that isocyanates having a carbonyl group adjacent to the cumulative double bonds may react as 1,4-dipolar reagents in cycloaddition reactions.[6] In this paper, reactions of phosphonium ylides with benzoyl isocyanate were studied.

The reaction of carbethoxymethylenetriphenylphosphorane (**1a**) with benzoyl isocyanate gave the stable ylide **2a** in good yield.



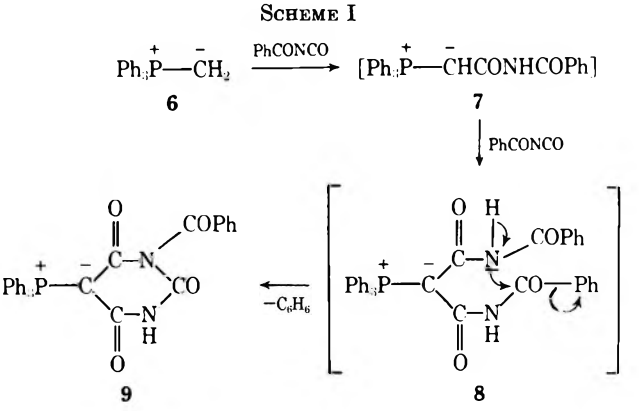
The nmr and ir spectra of the ylide **2a** showed N–H peaks at δ 12.67 ppm and 3200 cm^{-1}, respectively. The ylide **2a** was hydrolyzed easily to the ylide **3a**. Similar reactions were observed for phenylmethylenetriphenylphosphorane (**1b**).

In the reaction of the ylide **4** with an acyl group adjacent to the ylide carbon, the betaine **5** was obtained in high yield. The ir spectrum indicated no peak near 3200 cm^{-1}. The signal of the methine proton was observed at δ 1.68 ppm in the nmr spectrum of the betaine **5a**. The betaine **5** was easily decomposed to the starting ylide **4** and benzoyl isocyanate. Thus, in this reaction, a prototropic shift was not observed.



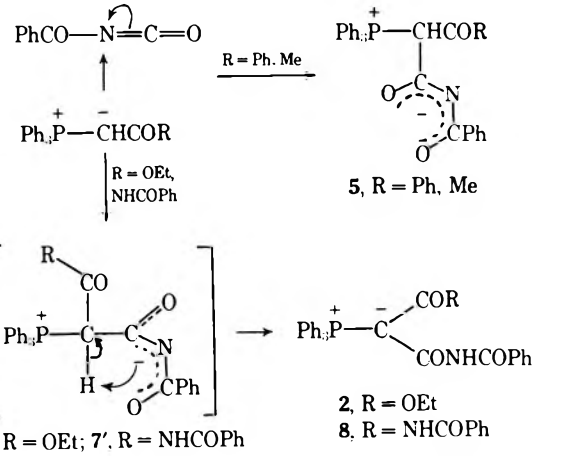
The reaction type for methylenetriphenylphosphorane (**6**) was similar to that of the ylide **1**. Benzoyl isocyanate (2 mol) was added to the ylide **6** with prototropic shifts, and the adduct **8** cyclized immediately to the ylide **9** (Scheme I). From the fact that

SCHEME I



the adduct **7** was not isolated, it seemed that the addition rate of the adduct **7** was very fast. 2,4,6-Triphenyl-1,3,5-triazine (**10**) was obtained as a by-product in this reaction.

In conclusion, the reaction between benzoyl isocyanate and an ylide which has a hydrogen atom on the ylide carbon gives a betaine in the initial step. The ease of the prototropic shifts can be correlated with the substituent constants,[7,8] σ_m and σ^+, of the substituent adjacent to the carbonyl group. It is apparent that the acidity of the betaine **1a′** or **7′** is higher than



(1) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, p 132.
(2) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 635 (1919).
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(5) F. Ramirez, J. F. Pilot, N. B. Desai, C. P. Smith, B. Hansen, and N. McKelvie, *J. Amer. Chem. Soc.*, **89**, 6273 (1967).
(6) H. Ulrich, "Cycloaddition Reaction of Heterocumulenes," Academic Press, New York, N. Y., 1967, p 203.
(7) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(8) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 95 (1963).

that of the betaine 5,[9] and thus the former give stable ylides and the latter gives a betaine.

Possibly the high acidity of the betaine in the case of the ylide **1b** is due to a resonance effect of the phenyl group.

Experimental Section

Materials.—Benzoyl isocyanate was prepared according to the procedure of Speziale:[10] bp 99–101° (20 mm); ir 2240 cm^{-1} (NCO).

The ylides 1a,[11] **4a**,[12] and **4b**[12] were prepared according to the known procedures. The physical properties were identical with reported data.

Reaction of the Ylide 1a.—Benzoyl isocyanate (0.02 mol) dissolved in 3 ml of benzene was added dropwise to 0.02 mol of the ylide 1a dissolved in 200 ml of benzene under a nitrogen stream. The mixture was stirred at 50° for 3 hr. The resulting precipitate was filtered off and recrystallized with methanol to give 6.0 g (93%) of the ylide **2a**: mp 195–196.5°; ir (Nujol) 3200 (NH), 1700, 1640, 1600 cm^{-1} (CO); nmr ($CDCl_3$) δ 0.52 (t, 3, J = 7.1 Hz, CH_3), 3.73 (q, 2, J = 7.1 Hz, CH_2), 12.62 (s, 1, NH); mol wt (vpo, $CHCl_3$) 498 (calcd 496).

Anal. Calcd for $C_{30}H_{26}O_4NP$: C, 72.72; H, 5.29; N, 2.83. Found: C, 72.95; H, 5.35; N, 2.86.

Hydrolysis of the Ylide 2a.—The ylide **2a** (1.5 g) was dissolved in 50 ml of EtOH, and a small quantity of NaOH was added. The mixture was refluxed for 10 hr, concentrated, extracted (benzene), and recrystallized (MeOH) to give 0.7 g (60%) of the ylide **3a**: mp 192–193°; ir ($CHCl_3$) 3560, 3360 (NH), 1620, 1600 cm^{-1} (CO); nmr ($CDCl_3$) δ 0.52 (t, 3, J = 7.5 Hz, CH_3), 3.69 (q, 2, J = 7.5 Hz, CH_2); mass spectrum (70 eV) m/e 391 (M^+, calcd 391), 347 ($Ph_3P{=}CCOOEt^+$), 319 ($Ph_3P{=}CHCOO^+$).

Anal. Calcd for $C_{23}H_{22}O_3NP$: C, 70.58; H, 5.66; N, 3.58. Found: C, 70.92; H, 5.81; N, 3.49.

Reaction of the Ylide 1b.—The mixture of 0.04 mol of phenyllithium, 0.03 mol of benzyltriphenylphosphonium chloride, and 150 ml of ether was stirred for 8 hr at room temperature under a nitrogen stream.[13] Benzoyl isocyanate (0.03 mol) was added dropwise, and stirring was continued for 7 hr. The reaction mixture was concentrated and recrystallized (benzene–methanol) to give 15.0 g (73%) of the ylide **2b**: mp 176.5–178°; ir ($CHCl_3$) 3440 (NH), 1690, 1610 cm^{-1} (CO); nmr ($CDCl_3$) δ 8.12 (b, NH, disappeared by D_2O addition); mass spectrum (70 eV) m/e 499 (M^+, calcd 499), 379 ($Ph_3P{=}C(Ph)$-CO^+), 351 ($Ph_3P{=}CPh^+$).

Anal. Calcd for $C_{33}H_{26}O_2NP$: C, 79.34; H, 5.25; N, 2.80. Found: C, 79.69; H, 5.24; N, 2.64.

Reaction of the Ylide 4a.—Benzoyl isocyanate (0.02 mol) was added dropwise to 0.02 mol of the ylide **4a** dissolved in 100 ml of toluene, and the mixture was stirred for 3 hr at 60° under a nitrogen stream. The resulting precipitate was recrystallized (MeOH–Et_2O) to give 9.5 g (90%) of the betaine **5a**: mp 169–170°; ir ($CHCl_3$) 1700, 1640, 1580 cm^{-1} (CO); nmr ($CDCl_3$) δ 1.68 (s, 1, CH); mass spectrum (70 eV) m/e 380 ($Ph_3P{=}$ $CHCOPh^+$), 147 ($PhCONCO^+$).

Anal. Calcd for $C_{34}H_{26}O_3NP$: C, 77.41; H, 4.98; N, 2.67. Found: C, 77.12; H, 4.92; N, 2.65.

Decomposition of the Betaine 5a. A.—The betaine **5a** (2.5 g) was heated at 180° for 15 min under reduced pressure (20 mm). Benzoyl isocyanate was trapped as benzamide. The residue was chromatographed (Al_2O_3, benzene) to give 1.55 g (86%) of the ylide **4a**.

B.—The ethanol solution of the betaine **5a** was refluxed for 7 hr in the presence of a small quantity of HBr. The ylide **4a** was recovered quantitatively.

Reaction of the Ylide 4b.—The ylide **4b** reacted with benzoyl isocyanate in the same manner as the ylide **4a** to give the betaine **5b**: yield 85%; mp 196.5–197.5° (recrystallized from MeOH–Et_2O); ir (Nujol) 1700, 1620, 1540 cm^{-1} (CO); mass spectrum (70 eV) m/e 318 ($Ph_3P{=}CHCOMe^+$), 147 ($PhCONCO^+$).

Anal. Calcd for $C_{29}H_{24}O_3NP$: C, 74.83; H, 5.20; N, 3.01. Found: C, 74.58; H, 4.94; N, 3.01.

Decomposition of the Betaine 5b.—The ethanol solution of the betaine **5b** was refluxed for 8 hr in the presence of a small quantity of NaOH. The ylide **4b** was recovered quantitatively by extraction with benzene.

Reaction of the Ylide 6.—The mixture of 0.01 mol of methyltriphenylphosphonium bromide, 0.01 mol of NaH, and 200 ml of THF was stirred for 8 hr.[14] After separation of the insoluble solid, 0.02 mol of benzoyl isocyanate was added dropwise, and stirring was continued for 7 hr at room temperature under a nitrogen stream. The reaction mixture was concentrated and extracted (benzene). Insoluble solid was recrystallized (MeOH–benzene) to give 2.2 g (43%) of the ylide **9**: mp 282–283°; ir (Nujol) 3420 (NH), 1750, 1700, 1640, 1600 cm^{-1} (CO); mass spectrum (70 eV) m/e 492 (M^+, calcd 492), 449 ($M^+ - HNCO$), 431 ($M^+ - CONHCO$), 147 ($PhCONCO^+$).

Anal. Calcd for $C_{29}H_{21}O_4N_2P$: C, 70.53; H, 4.30; N, 5.69. Found: C, 70.52; H, 4.26; N, 5.61.

The extract with benzene was recrystallized (benzene–hexane) to give 0.5 g (19%) of the triazine **10**: mp 239–240°; ir (Nujol) 1520 cm^{-1}, identical with that of the authentic sample;[15] mass spectrum (70 eV) m/e 309 (M^+, calcd 309).

Anal. Calcd for $C_{21}H_{15}N_3$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.50; H, 4.59; N, 13.56.

Registry No.—2a, 29411-29-8; **2b**, 29411-30-1; **3a**, 29520-63-6; **5a**, 29411-31-2; **5b**, 29250-64-7; **9**, 29411-32-3; benzoyl isocyanate, 4461-33-0.

Acknowledgment.—The authors thank Mr. Yutaka Ohno for his help in the experiments.

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(10) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28**, 1805 (1963).

(11) D. B. Denney and S. T. Ross, *ibid.*, **27**, 998 (1962).

(12) F. Ramirez and S. Dershowitz, *ibid.*, **22**, 41 (1957).

(13) G. Wittig and M. Rieber, *Justus Liebigs Ann. Chem.*, **562**, 177 (1949); ref 1, p 52.

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(15) S. Yanagida, H. Hayama, M. Yokoe, and S. Komori, *ibid.*, **34**, 4125 (1969).

Spontaneous Ring Enlargement during the Free-Radical Bromination of 2-Benzyl-1,3,3-trimethyl- and 2-Benzyl-3,3-dimethylbicyclo[2.2.1]heptanol-2

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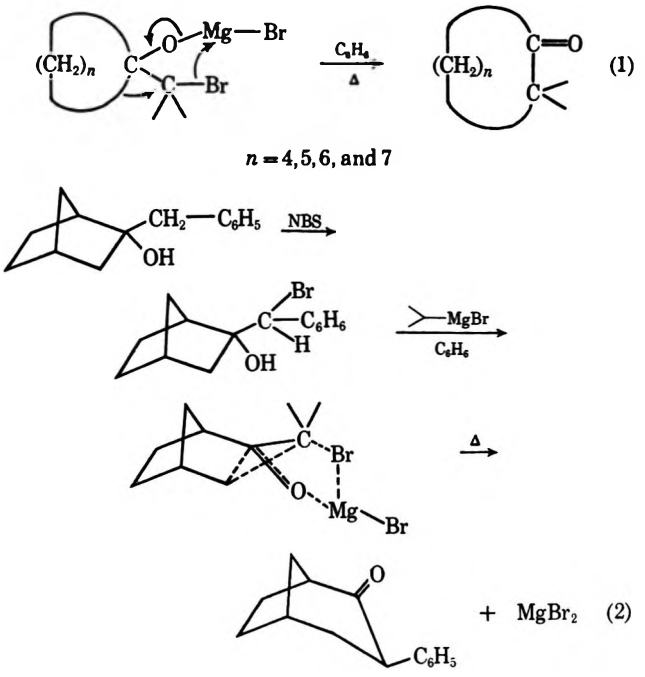
Previous publications[1] have reported a simple method by which one may effect a ring expansion, namely, through the decomposition of the magnesium salts of halohydrins with appropriate structures (eq 1). New examples[1b,d] (eq 2) were cited of the previously reported[2] anomalous migration (in the norbornyl system) of the *less*-substituted C-2–C-3 bond instead of the *more*-substituted C-1–C-2 bond to an incipient electron-deficient center.[3] The latter occurs even though the transition state proceeds through the less favorable boat conformation (eq 2) in preference to the chair conformation. It is apparent that one must consider some factor(s) opposing both electronic and boat form interactions in the transition state. Sauers[2] offered a rationale by proposing a third factor. The factor is

(1) A. J. Sisti, *J. Org. Chem.*, **33**, 453 (1968); (b) A. J. Sisti, *Tetrahedron Lett.*, No. 52, 5327 (1967); (c) A. J. Sisti, *J. Org. Chem.*, **33**, 3953 (1968); (d) A. J. Sisti, *ibid.*, **35**, 2670 (1970).

(2) R. R. Sauers and J. A. Beisler, *ibid.*, **29**, 210 (1964).

(3) Only the Baeyer–Villiger reaction of norbornanone-2 (migration to oxygen) is exceptional in that it alone is controlled by electronic factors (C-1–C-2 bond migration). J. A. Berson and S. Suzuki, *J. Amer. Chem. Soc.*, **81**, 4088 (1959), have concluded that migrations to oxygen should be most sensitive to electrical changes in the migrating groups.

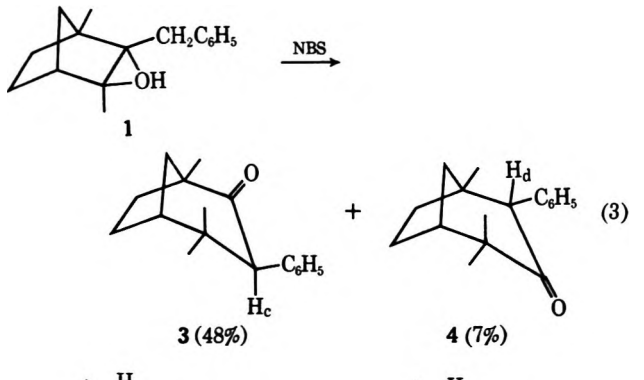


(1)

(2)

associated with the torsional strain resulting from the eclipsed nonbonded interactions between the substituents on C-2 and the hydrogens on C-3. Nonbonded interactions between the groups on C-2 and the bridgehead substituent are much less since the dihedral angles are 44 and 79°. Therefore, C-2–C-3 bond migration entails much more relief of eclipsing strain than C-1–C-2 bond migration.

Reported herein are two unusual examples which further substantiate the Sauers' postulate. When 2-benzyl-1,3,3-trimethylbicyclo[2.2.1]heptanol-2 (**1**) and 2-benzyl-3,3-dimethylbicyclo[2.2.1]heptanol-2[4] (**2**) were treated with *N*-bromosuccinimide and benzoyl peroxide in refluxing carbon tetrachloride, a spontaneous ring enlargement transpired (eq 3 and 4). The structural



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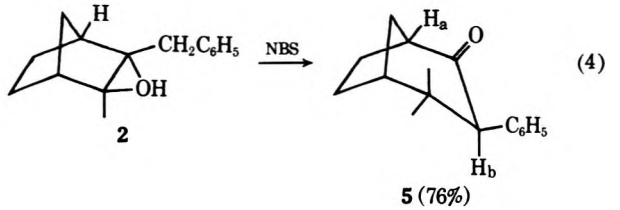
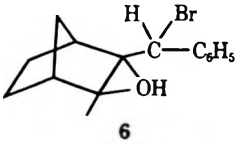


(4)

assignments for the ketones were based upon elemental analysis and infrared and mainly nmr analysis with the assistance of model compounds. The ketone **5** exhibited the following nmr signals: multiplet at τ 7.1–7.3 assigned to the bridgehead hydrogen α to a carbonyl group (H_a), a singlet at τ 6.60 ascribed to the benzyl hydrogen α to a carbonyl group (H_b) (migration of the C-1–C-2 bond in **2** would have resulted in the production of 4,4-dimethyl-2-phenylbicyclo[3.2.1]octanone-3 and not **5**; the former would have produced a doublet for the benzyl hydrogen α to a carbonyl group[5]), and signals for the methyl groups at τ 9.07 and 9.15. The model compounds employed for comparison were norbornanone-2, bicyclo[3.2.1]octanone-2, 3-methylbicyclo[3.2.1]octanone-2,[1d] and 3-phenylbicyclo[3.2.1]octanone-2[1b] with the bridgehead hydrogen α to the carbonyl group (all multiplets similar to H_a in **5**) at τ 7.30, 7.30, 7.35, and 7.25, respectively. The ketone **3** gave signals at τ 6.68 (benzyl hydrogen α to a carbonyl group H_c) and for the methyl groups at τ 8.89, 9.10, and 9.20. The product **4** exhibited signals at τ 6.45 (benzyl hydrogen α to a carbonyl group H_d) and the methyl groups at τ 9.18, 8.94, and 8.78. The τ values lower than 9, in each case, were attributed to the methyl groups on a carbon α to the carbonyl group. The model compounds from which the structural assignments were made were 3-methylbicyclo[3.2.1]octanone-2[1d] and **5**. The stereochemical assignment for the phenyl group assumes the more stable conformation as given in **3**, **4**, and **5**. The basis for the assignment was twofold: previous equilibration studies with 3-phenylbicyclo-[3.2.1]octanone-2[1b] and an equilibration study with **3** in trifluoroacetic acid.

The presence of the methyl groups (C-3, **1** and **2**) raises the magnitude of the unfavorable nonbonded interactions between the eclipsed groups on C-2 and C-3 resulting in an increase in the torsional strain (compared to the bromohydrin in eq 2 which is stable under the same preparative conditions). Thus, the release of strain supplies the driving force for the spontaneous decomposition (eq 3) during the free-radical bromination. It should also be noted that each compound, **1** and **2**, decomposes to the ring-enlarged ketones **3** and **5** as a result of the highly preferential migration of the C-2–C-3 bond over the C-1–C-2 bond. Particularly noteworthy is the result from the fenchone system, **1**, which apparently further substantiates the Sauers' postulate. The electronic effects are essentially equal, and competition is between proceeding through the more favorable chair form (migration of C-1–C-2 bond) *vs.* the less favorable boat form involving the release of torsional strain (migration of C-2–C-3 bond); the latter consideration predicts the observed major product, **3**, over **4**.

The possibility that the conversion of **1** and **2** to the ring-enlarged ketones (eq 3) might have involved an alkyl migration (C-2–C-3 bond) to a free-radical center was dampened by subsequent experimentation. The bromohydrin **6** was shown to be a reasonable inter-



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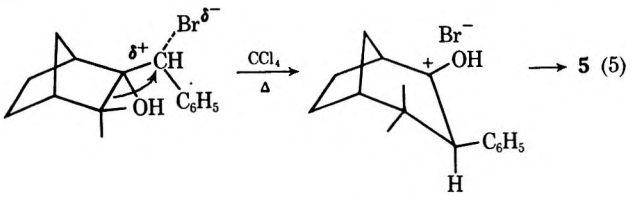
(4) Precedent argues that the stereochemical assignments of these alcohols is as presented in **1** and **2**, *exo*-2-benzyl groups and *endo*-2-ols (see ref 2).

(5) The doublet is expected from inspection of models; however, tangible support is offered from the nmr spectra of 2-phenyl-3-methylcyclohexanone and 2-phenyl-3-methylcycloheptanone doublets at τ 6.94 and 6.77, respectively (unpublished results).

mediate during the conversion of 2 to 5 (eq 4) by its synthesis from 2 with bromine in carbon tetrachloride (light catalyzed) at room temperature followed by its decomposition in refluxing carbon tetrachloride to 5. In addition, treatment of 2 in carbon tetrachloride with benzoyl peroxide gave no evidence of any products resulting from migration of an alkyl group to a free-radical center. The latter, coupled with the known reluctance of an alkyl group to migrate to a free-radical center,[6] leads one to an ionic interpretation for the production of the ring-enlarged ketones (eq 5). Lastly, a mechanism *via* an epoxide intermediate 7 was ruled out since none of the expected carbonyl compounds therefrom, 8 and 9, were detected.



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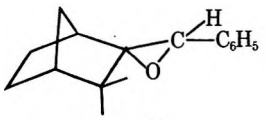

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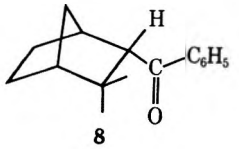

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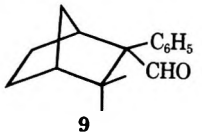

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Experimental Section[7]

2-Benzyl-1,3,3-trimethylbicyclo[2.2.1]heptanol-2 (1) and 2-Benzyl-3,3-dimethylbicyclo[2.2.1]heptanol-2 (2) were prepared by the dropwise additions of 80-ml ether solutions of fenchone and camphenilone (0.35 mol), respectively, into benzylmagnesium chloride (from 53 g of benzyl chloride, 11.4 g of magnesium, and 300 ml of ether). After the addition the solution was refluxed for 14 and 24 hr, respectively, and then decomposed (NH_4Cl). The separated organic portion was washed with water and dried ($MgSO_4$). After removal of the solvent under vacuum the alcohol 1 was distilled yielding 72 g (0.30 mol) (87%) of a liquid, bp 112–116° (0.2 mm). The alcohol was crystallized from aqueous ethanol after 1 month in the refrigerator: mp 57–59°; vpc (10% Carbowax on Chromosorb W, 142°, 40 psi) showed one peak; ir spectrum (CCl_4) 3590 cm^{-1} (OH); nmr (CCl_4) τ 7.23 (s, benzyl hydrogens).

Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.63; H, 9.94.

The alcohol 2 was crystallized and recrystallized from methanol yielding 71 g (0.30 mol) (89%), mp 45–47°. After three recrystallizations followed by vacuum drying (24 hr), it had mp 48–49.5°; ir spectrum (CCl_4) 3585 cm^{-1} (OH); nmr (CCl_4) τ 7.26 (s, benzyl hydrogens).

Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.51; H, 9.72.

4,4-Dimethyl-3-phenylbicyclo[3.2.1]octanone-2 (5).—A mixture of 5.75 g (0.025 mol) of 2, 4.8 g (0.027 mol) of *N*-bromosuccinimide, 75 ml of carbon tetrachloride, and 0.1 g of benzyl peroxide was refluxed for 2 hr. The mixture was then cooled and filtered and the filtrate was washed successively with water, 10% sodium carbonate, and water and dried ($MgSO_4$). The solvent was removed under vacuum and the residual solid was recrystallized from carbon tetrachloride yielding 4.3 g (0.190 mol) (76%) of a white solid 5: mp 139–140°; ir spectrum ($CHCl_3$) 1705 cm^{-1} (C=O); nmr (CCl_4) τ 6.60 (s, benzyl hydrogen α to a carbonyl group), 7.10–7.30 (m, bridgehead hydrogen α to a carbonyl group), 9.07 and 9.15 (s, two methyl groups on carbon α to a phenyl group).

Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 83.97; H, 8.67.

2-(α-Bromobenzyl)-3,3-dimethylbicyclo[2.2.1]heptanol-2 (6).—Into a 100-ml three-necked round-bottom flask was placed 42 ml of carbon tetrachloride and 5.75 g (0.025 mol) of 2. The flask was fitted with a thermometer, dropping funnel, and condenser (maintained nitrogen sweep during the entire reaction). Bromine, 4.0 g (0.025 mol), in 8 ml of carbon tetrachloride was added dropwise over a 2.5-hr period during which time the flask was irradiated (Sperti P106 uv lamp) and the temperature kept below 28°. The solution was then washed with water and 10% sodium carbonate and dried ($MgSO_4$). The solvent was removed from one-third of the solution yielding 2.13 g of a light yellow oil: positive silver nitrate; ir spectrum (film) 3550 cm^{-1} (OH); nmr (CCl_4) τ 4.70 (s, benzyl hydrogen).

The remaining solution was refluxed for 2 hr and then washed with 10% sodium carbonate and water and dried ($MgSO_4$). After removal of the solvent and three recrystallizations from pentane, there was obtained the ketone 5: 1.39 g (0.0061 mol) (38%); mp 141–142°; mixture melting point showed no depression; ir spectrum identical with that of 5.

Reaction of 2-Benzyl-1,3,3-trimethylbicyclo[2.2.1]heptanol-2 (1) with *N*-Bromosuccinimide.—Into a flask was placed 12.2 g (0.050 mol) of 1, 9.5 g (0.055 mol) of *N*-bromosuccinimide, 0.2 g of benzoyl peroxide, and 125 ml of carbon tetrachloride. The mixture was brought to reflux, at which time an extremely vigorous reaction occurred after which the mixture was refluxed for an additional 0.5 hr. The mixture was then cooled and filtered and the solvent removed under vacuum. Distillation of the residue yielded 8.15 g of product, bp 121–124° (0.10 mm), the nmr of which indicated a mixture of several components, primarily, 1,4,4-trimethyl-3-phenylbicyclo[3.2.1]octanone-2 (3) (48% based on 1) and a minor (5–10%) amount of 1,4,4-trimethyl-2-phenylbicyclo[3.2.1]octanone-3 (4) (yields based upon ratio of integrations of the benzyl hydrogens to the total integration of the phenyl hydrogens).

An aliquot (1.0 g) of the distillate was crystallized with pentane (7 ml) yielding *pure* 3: mp 49–51.5°; 0.48 g (30% based on 1); ir spectrum (CCl_4) 1710 cm^{-1} (C=O); nmr (CCl_4) τ 2.90–3.20 (m, phenyl hydrogens), 6.68 (s, benzyl hydrogen α to a carbonyl group), 8.89 (s, bridgehead methyl group on carbon α to a carbonyl group), 9.10 and 9.20 (s, methyl groups on carbon α to a phenyl group).

Anal. Calcd for $C_{17}H_{22}O$: C, 84.20; H, 9.15. Found: C, 84.20; H, 9.20.

The 2,4-dinitrophenylhydrazone had mp 161.5–162.5° (EtOH).

Anal. Calcd for $C_{23}H_{26}N_4O_4$: C, 65.39; H, 6.20; N, 13.26. Found: C, 65.28; H, 6.16 N, 13.39.

The nmr analysis of the previous filtrate revealed that an additional 0.2 g of 3 was present [total 3, 0.69 g (46% based upon 1)].

An aliquot (2.0 g) of the original distillate was now chromatographed (100 g of Woelm acid washed alumina, grade I) with the following results. Elution with 150 ml of hexane gave a pure sample of 2-benzylidene-1,3,3-trimethylbicyclo[2.2.1]heptane (dehydration product from 1), 0.24 g (12% based on 1). The structural assignment was based upon ir spectrum (film) 1663 cm^{-1}; nmr (CCl_4) τ 3.88 (s, vinyl hydrogen). Final elution (200 ml of benzene followed by 400 ml of chloroform) gave a mixture of 3 and 4 which resisted separation. Examination of the nmr (CCl_4) revealed the presence of the ketone 4: nmr τ 6.45 (s, benzyl hydrogen α to a carbonyl group), 8.78 and 8.94 (s, methyl groups on a carbon α to a carbonyl group), 9.18 (s, bridgehead methyl on a carbon α to a phenyl group). Based upon the integration of the benzyl hydrogen in 4 relative to the benzyl hydrogen in 3 and to the total phenyl hydrogens in the sample, it was estimated that 4 represented 10% of the sample (7% based on 1). The ketone 3 represented 70% of this sample (47% based on 1).

Reaction of 2-Benzyl-3,3-dimethylbicyclo[2.2.1]heptanol-2 (2) with Benzoyl Peroxide.—Into a flask was placed 2.30 g (0.01 mol) of 2 2.42 g (0.01 mol) of benzoyl peroxide, and 25 ml of carbon tetrachloride. The mixture was refluxed for 24 hr followed by removal of the solvent under vacuum. The residue was dissolved in pentane and washed with a 10% solution of sodium

(6) C. Walling in "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 407.

(7) All melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Spectracord infrared spectrophotometer. The nmr spectra were determined with a Varian A-60 instrument.

carbonate. The solvent was removed under vacuum and gave no evidence of the presence of ketone **5** as confirmed by the ir spectrum (no C=O absorption at 1705 cm^{-1}), and nmr (CCl_4) showed no benzyl hydrogen at τ 6.60.

Registry No.—**1**, 29478-03-3; **2**, 29478-04-4; **3**, 29478-05-5; **3** 2,4-DNP, 29478-06-6; **5**, 29478-07-7; **6**, 29478-08-8; *N*-bromosuccinimide, 128-08-5.

Halogenated Ketenes. XX. Substitution *vs.* Rearrangement of Halogenated Ketene Olefin Cycloadducts[1,2]

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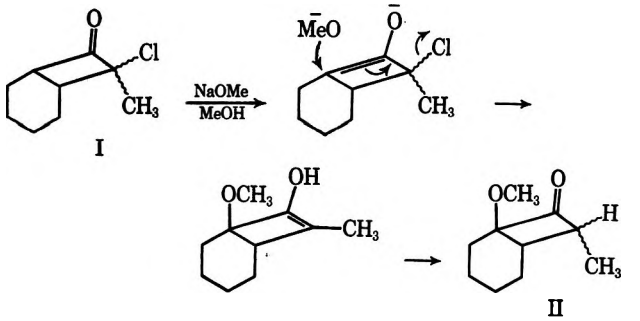
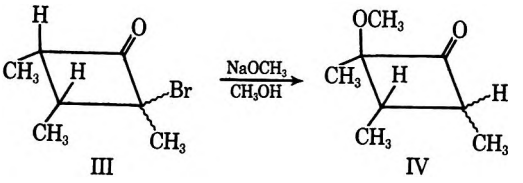
Received November 4, 1970

Two communications have recently appeared which describe a base-catalyzed rearrangement of a cycloadduct of a halogenated ketene and an olefin leading to a bifunctional cyclopropane.[3,4] These reports prompt us to describe our results on the rearrangement of a bicyclo[3.2.0]hept-2-en-6-one ring system to the bicyclo[3.1.0]hex-2-ene ring system in the presence of sodium methoxide in refluxing methanol. This ring system undergoes rearrangement in contrast to other systems studied by us and other workers which undergo substitution under similar conditions.

Fletcher and Hassner have reported that the dichloroketene adducts of cholestene and cyclohexene undergo rearrangement under the influence of methoxide to produce 1-methoxy-7-carbomethoxybicyclo[4.1.0]-heptane in the latter case and the corresponding rearranged product in the former. A proposed mechanism involves enolization, followed by methoxy substitution on C_6 (this intermediate was isolated) and subsequent loss of the second chlorine atom and rearrangement to the bicyclo[4.1.0]heptane derivative.

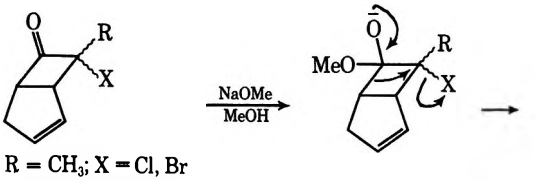
When the adduct of methylchloroketene and cyclohexene (I) was treated with a threefold excess of sodium methoxide in refluxing methanol, II was obtained in approximately 60% yield as the only volatile product. This compound corresponds to Hassner's intermediate, except that in this case a second leaving group is not



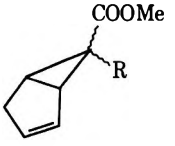


available for further rearrangement. Similarly, when the adduct of methylbromoketene and *cis*-2-butene (III) was treated with methoxide, the substitution product (IV) was obtained in 70% yield.

However, when the methylchloro- or methylbromoketene adduct of cyclopentadiene (V) was heated with



Va, R = CH_3; X = Cl, Br
b, R = H; X = Cl, F
c, R = vinyl; X = Br

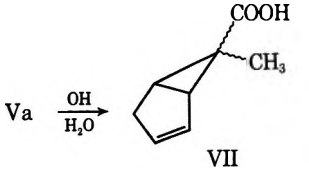


VIa, R = CH_3
b, R = H
c, R = vinyl

sodium methoxide in methanol, rearrangement occurred rather than substitution. The methoxide ion attacks the carbonyl carbon atom, thus leading to the rearranged product (VI). This is consistent with the mechanism proposed by Brook, *et al.*, and is formally analogous to the Favorski rearrangement of α-haloketones.[4,5] This rearrangement was observed with several halogenated ketene–cyclopentadiene adducts as illustrated.

The structure of VI was established by elemental analysis, infrared spectra and the following nmr and and mass spectral data. The chemical shift of the bridgehead protons in the nmr spectra of VI ranged from δ 1.0 to 2.5, and the corresponding bridgehead protons in the bicyclo[3.2.0]hept-2-en-6-ones appear at δ 3.5–4.3;[6] the chemical shift of the ester methoxy protons occurred at a position characteristic of an ester (δ 3.5–3.7) rather than at a position characteristic of an ether (δ 3.2–3.3). A parent peak at *m/e* 152 for VIa was observed in the mass spectrum; a very intense peak was also observed at *m/e* 93 resulting from the loss of a carbomethoxy group.

As a further verification of the structure of VIa, Va was treated with 20% aqueous sodium hydroxide solution, resulting in the formation of a carboxylic acid (VII). This acid was converted to the methyl ester by treatment with thionyl chloride and then methanol.



VII

(1) Paper XIX: W. T. Brady and J. P. Hieble, *Tetrahedron Lett.*, 3205 (1970).

(2) Support of this investigation by The Robert A. Welch Foundation, National Science Foundation (GP-14016), and a North Texas State University Faculty Research Grant is gratefully acknowledged.

(3) V. R. Fletcher and A. Hassner, *ibid.*, 1071 (1970).

(4) P. R. Brook, J. M. Harrison, and A. J. Duke, *Chem. Commun.*, 589 (1970).

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The ester produced in this manner was identical with VIa as evidenced by nmr, ir, and mass spectra.

In the rearrangement reactions of V, the rearranged products (VI) were the only products isolated from the reaction mixtures. There was considerable polymer and tar formation in some of the systems resulting in a low yield of rearranged product. There was some indication of trace amounts of the product resulting from methoxy substitution on C_5; however, there was no evidence for direct methoxy substitution on C_7.

The adducts of nonhalogenated ketenes and cyclopentadiene (either aldoketene or ketoketene adducts) were inert to the reaction conditions used to produce the above rearrangements. However, some isomerization was observed in the aldoketene adducts.

The tendency for cyclopentadiene adducts to undergo rearrangement, to the exclusion of substitution on C_5, can be explained by considering the stability of the enol formed by the loss of the bridgehead hydrogen adjacent to the carbonyl. This enol must be formed to account for substitution at this carbon. It is obvious that this enol would be more stable in the *cis*-2-butene and cyclohexene adducts than in the adducts of cyclopentadiene, owing to the increased amount of strain in the latter system because of the double bond on the bridgehead carbon.

Therefore, the treatment of halogenated ketene–olefin cycloadducts with sodium methoxide results in substitution. This substitution is dependent on enolization and, when the enolization is retarded, a Favorskii-type rearrangement occurs.

Experimental Section

We have previously described the preparation of the following cycloadducts: methylchloro- and methylbromoketene–cyclopentadiene (Va),[6] chloro- and fluoroketene–cyclopentadiene (Vb),[7] and methylchloroketene–cyclohexene (I).[8] 2,3-Dibromobutanoyl chloride was obtained by the bromination of crotonic acid and subsequent reaction with thionyl chloride.

2-Bromo-2,3,4-trimethylcyclobutanone (III).—A 20-g (0.12 mol) portion of 2-bromopropanoyl chloride was added dropwise with vigorous stirring to a solution of 25 ml (0.2 mol) of triethylamine and 80 ml (1 mol) of *cis*-2-butene in 200 ml of dry hexane at 0°. The reaction flask was fitted with a cold-finger condenser filled with Dry Ice–acetone to prevent loss of *cis*-2-butene. The reaction mixture was allowed to stand for 3 hr and then the amine salt was removed by filtration. Concentration on a rotatory evaporator and distillation afforded 5 g (22%): bp 40–42° (0.1 mm); ir 1800 cm^{-1}; nmr (CCl_4) (both isomers) δ 1.1 (d, 6 H, J = 8 Hz), 1.68 and 1.87 (two s, 3 H), 2.48 (m, 1 H), and 3.45 (m, 1 H).

Anal. Calcd for $C_7H_{11}BrO$: C, 43.9; H, 5.75. Found: C, 43.83; H, 5.50.

7-Bromo-7-vinylbicyclo[3.2.0]hept-2-en-6-one (Vc).—A 66-g (0.25 mol) portion of 2,3-dibromobutanoyl chloride was added dropwise with vigorous stirring to a solution of 35 ml (0.25 mol) of triethylamine and 80 ml (1 mol) of cyclopentadiene in 200 ml of dry hexane at 0–5°. This mixture was stirred overnight and then filtered to remove the amine salt. The filtrate was concentrated on a rotatory evaporator and distilled. The cycloadduct initially formed dehydrobrominated readily and, after three distillations, the vinylbromoketene–cyclopentadiene adduct was obtained: bp 80–82° (1 mm); ir 1800 and 1650 cm^{-1}; nmr (CCl_4) δ 2.7 (m, 2 H), 4.0 (m, 2 H), and 5.6 (m, 5 H).

Anal. Calcd for C_9H_9BrO: C, 50.73; H, 4.26. Found: C, 50.43; H, 4.61.

General Procedure for Sodium Methoxide Treatment of Cycloadducts.—A 150-ml portion of methanol to which 4 g of sodium had been added was vigorously refluxed while a solution of 10 g of the ketene–olefin cycloadduct in 25 ml of methanol was added. There was an immediate precipitation of the sodium halide with all of the halogenated ketene adducts. Refluxing was continued for 15 min and then the mixture was added to 150 ml of water. This aqueous mixture was extracted with chloroform. After the combined extracts were dried, the solvent was removed on a rotatory evaporator and the residue was distilled to yield the product.

8-Methyl-6-methoxybicyclo[4.2.0]octan-7-one (II).—A 60% yield was obtained: bp 56–58° (1.8 mm); ir 1780 cm^{-1}; nmr (CCl_4) δ 1.15 (d, 3 H, J = 8 Hz), 1.8 (m, 10 H), and 3.45 (s, 3 H).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.3; H, 9.52; mol wt, 168. Found: C, 70.5; H, 9.17; mol wt (mass spectrum), 168.

2-Methoxy-2,3,4-trimethylcyclobutanone (IV).—A 70% yield was obtained: bp 98–100° (60 mm); ir 1780 cm^{-1}; nmr (CCl_4) δ 1.2 (m, 9 H), 2.1 (m, 2 H), and 3.2 (s, 3 H).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.50; H, 9.85. Found: C, 67.14; H, 9.78.

***endo*-6-Carbomethoxy-*exo*-6-methylbicyclo[3.1.0]hex-2-ene (VIa).**—About a 60% yield was obtained from either the methylchloroketene–cyclopentadiene adduct or the methylbromoketene–cyclopentadiene adduct: bp 60–62° (2 mm); ir 1740 cm^{-1}; nmr (CCl_4) δ 1.3 (s, 3 H), 1.6 (m, 1 H), 2.0 (m, 1 H), 2.6 (m, 2 H), 3.55 (s, 3 H), and 5.52 (m, 2 H); mass spectrum parent peak at 152 (theory 152), major peak at 93 (VIa − carbomethoxy).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.0; H, 7.9. Found: C, 70.97; H, 8.26.

6-Carbomethoxybicyclo[3.1.0]hex-2-ene (VIb).—A 15% yield was obtained from the chloroketene–cyclopentadiene adduct and a 10% yield from the corresponding fluoroketene adduct: bp 55° (2.5 mm); ir 1730 cm^{-1}; nmr (CCl_4) (both isomers) δ 2.3 (complex m, 5 H), 3.58 and 3.7 (two s, 3 H), and 5.7 (m, 2 H).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.5; H, 7.25. Found: C, 69.49; H, 7.52.

6-Carbomethoxy-6-vinylbicyclo[3.1.0]hex-2-ene (VIc).—A 15% yield was obtained: bp 70–72° (2.5 mm); ir 1730 and 1630 cm^{-1}; nmr (CCl_4) (both isomers) δ 2.4 (m, 5 H), 3.58 and 3.64 (2 s, C H), and 5.4 (m, 5 H).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.1; H, 7.31. Found: C, 72.6; H, 7.89.

6-Carboxy-6-methylbicyclo[3.1.0]hex-2-ene (VII).—A 10-g (0.06 mol) portion of Va was added to 200 ml of 20% aqueous NaOH solution and the resulting mixture was refluxed for 16 hr. After the mixture was cooled and acidified with dilute HCl solution, the product was extracted into chloroform. The combined extracts were dried and concentrated on a rotatory evaporator. Distillation afforded 5 g (60%) of VII: bp 100–102° (0.2 mm); mp 40–45° (solidification occurred in the receiver); nmr (CCl_4) δ 1.05 and 1.4 (2 s, 3 H), 2.6 (m, 4 H), 5.7 (m, 2 H), and 11.8 (s, 1 H).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.6; H, 7.25. Found: C, 69.81; H, 7.50.

Registry No.—II, 29494-54-0; III, 29478-01-1; IV, 29478-02-2; Vc, 29494-55-1; VIa, 29494-56-2; VIb, 29494-57-3; VIc, 29494-58-4; VII, 29494-59-5.

(7) W. T. Brady and E. F. Hoff, Jr., *J. Amer. Chem. Soc.*, **90**, 6256 (1968).
(8) W. T. Brady and R. Roe, Jr., *ibid.*, **93**, 1662 (1971).

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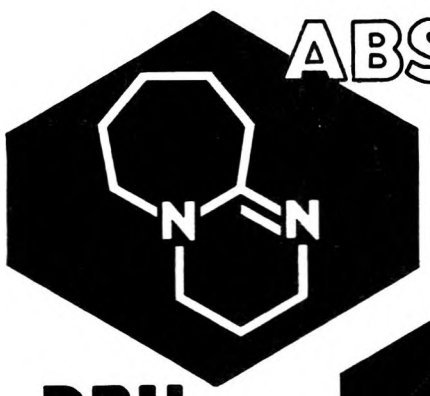
72A

THE ABSTRACTORS



DBU

PROTON-SPONGE*

DBN

PROTON SPONGE* is a remarkably strong base, pk_a 12.3 as described by Alder[1] and yet almost completely non-nucleophilic. Therefore, the olefins produced by the use of this reagent are free from substitution products which are sometimes produced in the reactions of DBU and DBN, (described below), particularly with primary tosylctes. Its rate of elimination in DMF is comparable to that of DBU and DBN. Dr. Alder[2] believes that its non-nucleophilicity will make it useful in many reactions, for instance, the formation of cyclopropanes and—perhaps of greatest interest—the deprotonation of ligands on metals, where many bases cause ligand displacement.

DBU[3] and DBN[4,5,6] have been shown to be very versatile dehydrohalogenating agents. As both are much more reactive than the amines generally used, much milder conditions can be employed, and even generally unstable compounds such as α,β-unsaturated terminal acetylenes have been prepared. Several most interesting compounds such as isobombycol, the sexual attractant of the female silk worm,[6] and some important intermediates in the preparation of the royal jelly of the honeybee,[5] are among the first of many ethylenes and acetylenes to be made with DBN. The yields with DBU are particularly high (e.g. 91% 3-heptene from 4-bromoheptane) and its use simple — a mixture of equimolar amounts of, say, bromoalkane and DBU with or without a solvent such as dimethyl sulfoxide is warmed to 80-90°, and the alkene is distilled.

1. R. W. Alder et al., Chem. Comm., 723 (1968).
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3. H. Oediger and F. Möller, Angew. Chem., 79, 53 (1967).
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6. E. Truscheit and K. Eiter, Ann., 658, 65 (1962).

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